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Using discrete choice modeling to evaluate the preferences and willingness to pay for leptospirosis vaccine

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Leptospirosis is highly endemic in the Philippines and a serious concern to public health. Local research on candidate vaccine is moving through the development pipeline. The availability of vaccines alone does not guarantee acceptance because individuals' vaccination choice decision is influenced by several factors. This study assessed how vaccine attributes and socio-demographic factors affect the acceptability of leptospirosis vaccine; and estimated individuals' willingness to pay for leptospirosis vaccine. A discrete choice experiment was conducted among leptospirosis and non-leptospirosis case respondents (n = 342) living in Metro Manila. Random Parameters Logit model was used to estimate the relative importance of vaccine attributes and socio-demographic variables on respondents' leptospirosis vaccination choice decision. The estimated model coefficients were used to derive implicit prices and willingness to pay for leptospirosis vaccine. Both case respondents preferred leptospirosis vaccine with 70–100% efficacy, mild to moderate risk of side-effects, given in a single shot, and at a lower price. Non-leptospirosis case respondents preferred a vaccine with 7 to 10 y of protection, while leptospirosis case respondents preferred a vaccine with 10 y protection. The probability of leptospirosis vaccination acceptance was affected by respondents' age, education, family size and income, proximity of home to rivers and sewers, and leptospirosis awareness level. Respondents' willingness to pay for leptospirosis vaccine (US$ 31.14–US$ 65.89) was higher than the Japanese retail price (US$ 21.60-US$ 24.00). Our findings indicated significant potential for introducing leptospirosis vaccine in the Philippine vaccine market. Delivery strategies to ensure equitable access to future leptospirosis vaccine are recommended.

Introduction

Leptospirosis is caused by pathogenic *Leptospira* bacteria that are transmitted from animal reservoirs to humans. The bacteria are eliminated through the urine of the infected hosts such as rats, livestock and domestic pets.[1] Humans may be infected by direct contact with infected urine or indirect contact with contaminated water or soil.[2] The infection can range from a mild flu-like illness to life-threatening complications such as jaundice, meningitis, hemorrhage, or renal dysfunction.[1,3] Leptospirosis is an emerging public health problem in the Philippines because of its increasing incidence associated with the growth of urban slums, inadequate waste disposal, occurrence of frequent typhoons, and expansion of flooding areas which have created ecological conditions for rat-borne disease transmission.[3,4] One of the most notable leptospirosis outbreaks occurred in 2009 after Typhoon *Ondoy* caused widespread flooding in Metro Manila, resulting in 2,089 cases of infection and 162 leptospirosis-related deaths.[5] A more recent study reported that the rate of leptospirosis incidence in Metro Manila has reached at 10,655 per 100,000 person-year.[6]

Vaccination can reduce the incidence and mortality associated with leptospirosis. However, human leptospirosis vaccines are commercially available only in few countries like France, Cuba and Japan.[7-10] Human leptospirosis vaccine is not commercially available in the Philippines, but the prospect for vaccine development is promising following the recent cooperation program with Japan to develop intervention measures for the prevention of leptospirosis. Nonetheless, it is important to understand that vaccine being available does not guarantee uptake considering that there are other factors that influence individuals' vaccination decisions. Some individuals may choose vaccination despite a high price or potential side effects, while others forego disease protection because of low income or to avoid side effects.

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Considering that individual decisions may be affected by preferential tradeoffs on whether or not to get vaccinated, the knowledge on individuals' preferences for vaccine is important in determining key attributes that are likely to impact the acceptability of the vaccine. Likewise, the estimates of willingness to pay (WTP) allow individuals' preferences to be expressed in monetary value that could be used for cost-benefit analysis of health care interventions, pricing strategy and demand analysis.[11,12]

Discrete Choice Experiment (DCE) is one quantitative approach that is increasingly being used in health economics to determine preferences and welfare estimates on health matters. DCE requires individuals to make choices based on hypothetical scenarios describe in terms of attributes and levels, and their responses are used to infer the value placed on each attribute[13]. The responses can be modeled using utility function to estimate the relative importance of each attribute, trade-offs between attributes, and the benefit respondents derived from the chosen scenario.[14] DCE has recently been applied to examine the acceptability of different vaccines such as varicella,[15] human papillomavirus,[16,17] and human immunodeficiency virus.[18,19] To date, no studies have examined the acceptability of human leptospirosis vaccine especially in the Philippines where the disease is highly endemic. Hence, this study utilized DCE method to assess the preferences and to estimate willingness to pay for future leptospirosis vaccine among urban residents in Manila, Philippines. The findings of this study may serve as policy guide to public health authorities and vaccine manufacturers in making investment decisions on leptospirosis vaccine development, in making research management decisions by highlighting how vaccine attributes may impact acceptability, and in developing appropriate strategies for leptospirosis vaccine delivery.

Results

Socio-demographic characteristics of the respondents

A total 114 leptospirosis case individuals and 228 non-leptospirosis case individuals participated in this study. As shown in **Table 1**, the average age of non-leptospirosis case respondents (37.93 years) was significantly higher than leptospirosis case respondents (34.90 years) at 5% level. While there were relatively more male than female respondents, the proportion of male respondents were significantly higher in leptospirosis case (90%) than non-leptospirosis case (60%) respondents at 1% level. There were no significant differences in terms of education, family size, and household income between the 2 case respondents. Leptospirosis and non-leptospirosis case respondents had an average family size of about 5 persons, and completed an average of about 10 y of education or equivalent to high school diploma. Their household incomes ranged from 2,800 to 80,000 pesos ($US 67.20 to US$ 1,920) a month. Leptospirosis case respondents received an average monthly income of 16,950 pesos (US$ 406.80), while non-leptospirosis respondents received an average monthly income of 18,900 pesos (US$ 453.60). The proportion of leptospirosis case respondents (83%) living near to a sewer (about 10 m) were significantly higher than non-leptospirosis case respondents (72%) at 5% level. Nearly equal proportion of leptospirosis (62%) and non-leptospirosis (64%) case respondents were living near to a river. While a slightly higher proportion of leptospirosis case respondents (75%) were living near to a sewer than non-leptospirosis case respondents (65%), there difference was not statistically significant at 5% level. Leptospirosis case respondents (93%) exhibited significantly higher awareness on the cause of leptospirosis, mode of transmission, symptoms and prevention of leptospirosis than non-leptospirosis case respondents (83%) at 1% level.

Table 1. Socio-demographic characteristics of the 2 case respondents

		Leptospirosis case Respondents n=114 [1]	Non-Leptospirosis case Respondents n=228 [2]	Difference [1]-[2]
Variable	**Description**	**Average (S.D)**	**Average (S.D)**	**($\|t\|$-Ratio)**
AGE	Age of the respondent in years	34.90 (13.64)	37.93 (12.59)	−3.03** (1.99)
EDUCATION	Years of education	9.97 (2.41)	10.28 (2.02)	−0.31* (1.18)
FAMILYSIZE	Number of persons in a household	5.17 (2.02)	5.08 (1.98)	0.09 (0.39)
INCOME	Household income ('000 pesos/month)	16.95 (11.96)	18.90 (11.64)	−1.95 (1.43)
MALE	Dummy: 1 = male respondent; 0 = female	0.90 (0.30)	0.60 (0.50)	0.31*** (7.20)
MARKET	Dummy: 1 if home is located near to a market (about 10 m);0 if far	0.83 (0.37)	0.72 (0.45)	0.11** (2.39)
RIVER	Dummy: 1 if home is located near to a river (about 10 m);0 if far	0.62 (0.49)	0.64 (0.48)	−0.02 (0.31)
SEWER	Dummy: 1 if home is located near to a sewer (about 10 m);0 if far	0.75 (0.44)	0.65 (0.48)	0.10 (1.79)
AWARENESS	Leptospirosis awareness score	0.93 (0.18)	0.83 (0.23)	0.10*** (4.25)

Note: ***denotes statistical significance at 1% level and **5% significance level.

Preferences for leptospirosis vaccine

The respondents' choice responses were analyzed by Random Parameters Logit (RPL) model allowing the coefficients of observed variables to vary randomly over the respondents rather than being fixed. **Table 2** reports the results of the RPL model estimation for leptospirosis case (Model 1) and non-leptospirosis case (Model 2) respondents. The two models were statistically significant at the 1% level with χ^2 statistics of 1,274.252 and 1,941.104 against a critical value of 40.113 with 27 degrees of freedom. The McFadden R^2 values (0.424 and 0.323) for the 2 models satisfied the conventional goodness-of-fit values of 0.2 to 0.4 commonly used to describe probabilistic choice models [20]. The coefficient estimates from the pooled dataset (Model 3) containing the observations of both the leptospirosis and non-leptospirosis case respondents were also statistically significant at the 1% level with χ^2 statistics of 3080.741 against a critical value 40.113 with 27 degrees of freedom. The value of the log-likelihood (*LL*) ratio comparing the pooled model ($LL = -2968.330$) against the separate models for leptospirosis case ($LL = -865.776$) and non-leptospirosis case ($LL = -2035.25$)

Table 2. Results of the Random Parameters Logit (RPL) model estimation

	Model 1: Leptospirosis case Respondents		Model 2: Non-leptospirosis case Respondents		Model 3: Pooled data set	
Variables	**Coeff.**	**Std. Err.**	**Coeff.**	**Std. Err.**	**Coeff.**	**Std. Err.**
Random parameters of vaccine attributes in the model						
EFFICACY of 50–60%[a]	−2.842***	0.318	−2.157***	0.193	−2.270***	0.154
EFFICACY of 70–80%	0.607***	0.126	0.442***	0.079	0.479***	0.057
EFFICACY of 90–100%	2.235***	0.256	1.715***	0.142	1.791***	0.127
PROTECTION of 2 years[a]	−0.521***	0.318	−0.531***	0.077	−0.500***	0.063
PROTECTION of 7 years	0.108***	0.118	0.242***	0.065	0.144***	0.054
PROTECTION of 10 years	0.413***	0.116	0.289***	0.064	0.356***	0.054
SERIOUS RISK of side effects[a]	−0.963***	0.130	−0.401***	0.075	−0.559***	0.062
MODERATE RISK of side effects	0.337***	0.121	0.159***	0.066	0.195***	0.052
MILD RISK of side effects	0.626***	0.129	0.242***	0.066	0.364***	0.055
Given in 3 SHOTS[a]	−0.580***	0.154	−0.506***	0.129	−0.453***	0.097
Given in 2 SHOTS	0.068***	0.296	0.164***	0.190	0.077***	0.149
Given in 1 SHOT	0.512***	0.188	0.342***	0.109	0.376***	0.087
Non-random main effects parameters of vaccine attributes in the model						
Alternative Specific Constant	2.424***	0.994	0.255	0.476	0.317	0.395
Price	−3.167***	0.403	−3.548***	0.251	−3.291***	0.172
Socio-demographics & Alternative Specific Constant (ASC) interaction in the model [b]						
AGE*ASC	−0.002	0.008	−0.010***	0.004	−0.007	0.004
EDUCATION*ASC	−0.067	0.046	0.058***	0.028	0.121	0.022
FAMILYSIZE*ASC	−0.082	0.520	−0.060***	0.028	−0.042	0.024
INCOME*ASC	0.015	0.011	0.012***	0.012	0.010***	0.004
MALE*ASC	0.121	0.422	0.200	0.199	0.527***	0.103
Living near to a MARKET*ASC	0.265	0.281	0.063	0.063	0.148	0.109
Living near to a RIVER*ASC	−0.063	0.233	0.419***	0.119	0.219***	0.102
Living near to a SEWER*ASC	−0.975***	0.282	−0.232***	0.118	−0.314***	0.107
Leptospirosis AWARENESS*ASC	1.216***	0.568	0.680***	0.235	1.040***	0.209
Derived Standard deviations of the parameter distributions						
EFFICACY of 70–80%	0.105	9.473	0.041	3.854	0.012	0.167
EFFICACY of 90–100%	1.114***	0.301	0.331	0.597	0.517	0.619
PROTECTION of 7years	0.070	2.414	0.004	5.776	0.006	0.168
PROTECTION of 10 years	0.027	4.160	0.374	0.441	0.764	0.236
MODERATE RISK of side effects	1.080***	0.353	0.010	1.158	0.338***	0.251
MILD RISK of side effects	0.071	2.372	0.004	4.007	0.060	0.167
Given in 2 SHOTS	0.443	1.407	0.009	4.906	0.011***	0.232
Given in 1 SHOT	0.209	1.384	0.968	0.198	0.703***	0.209
Log-likelihood	−865.776		−2035.251		−2968.334	
McFadden R^2	0.424		0.323		0.342	
No of parameters	27		27		27	
χ^2 statistics	1274.252***		1941.104***		3080.741***	
No of observation	1368		2736		4104	

Notes: ***denotes statistical significance at 1% level and **5% significance level. [a]Base attribute level. Its coefficient was derived as the negative sum of the coefficients of the other 2 alternative attribute levels. [b]The interaction terms indicate which respondents' characteristics affect the likelihood of accepting the leptospirosis vaccination program.

respondents was estimated at 134.614, which exceeded the critical value of χ^2 distribution of 40.113 with 27 degrees of freedom. Subsequently, the null hypothesis that the separate effects of the 2 respondent models are equal to zero was rejected at the 5% significant level. Hence, the leptospirosis case and non-leptospirosis case respondents have distinct preferences for vaccine attributes, and their preferences cannot be pooled together.

As shown in Model 1 of **Table 2**, leptospirosis case respondents preferred leptospirosis vaccine with 70–80% and 90–100% efficacies against 50–60% efficacy; with 10 y protection against 2 y of protection; with moderate and mild risk of side-effects against serious risk of side-effects; and a single shot against a 3-shot vaccine. However, they were indifferent between leptospirosis vaccine with 7 y of protection and 2 y of protection; and between a 2-shot and a 3-shot vaccine. Similarly, non-leptospirosis case respondents in Model 2 preferred a leptospirosis vaccine with 70–80% and 90–100% efficacy levels over 50–60% efficacy level; with 7 and 10 y of protection against 2 y of protection; with moderate and mild risk of side-effects over serious risk of side-effects; and a single shot over a 3-shot vaccine. They were indifferent between a 2-shot and a 3-shot leptospirosis vaccine. Finally, the significant and negative coefficients of price for both case respondents indicated that the likelihood of accepting the leptospirosis vaccine increased when price decreased.

The interaction between socio-demographic variables and Alternative Specific Constant (ASC) showed preference heterogeneity in the responses of the respondents. As shown in Model 1 of **Table 2**, leptospirosis case respondents living far from a sewer and with higher level of leptospirosis awareness were likely to accept the leptospirosis vaccination program against those respondents living near to a sewer and with lower level of leptospirosis awareness. The results in Model 2 indicated that non-leptospirosis case respondents with higher level of education, higher income, living near to a river and with higher level of leptospirosis awareness were more likely to accept the leptospirosis vaccination program against those with lower level of education, lower income, living far from a river and with lower level of leptospirosis awareness. However, non-leptospirosis case respondents of older age, with larger family size, and living near to a sewer were less likely to accept the leptospirosis vaccination program against those of younger age, with smaller family size and living far from a sewer.

Implicit prices of leptospirosis vaccine attributes

Table 3 shows the implicit price estimates for each of the non-monetary attributes of the leptospirosis vaccine. The implicit prices indicate the respondents' marginal willingness to pay from the least attractive (base) level to the next improved level attribute of the vaccine. For leptospirosis case respondents, efficacy was the highest valued leptospirosis vaccine attribute. Compared to the base levels, they were willing to pay 1,089.04 pesos (CI: 850.49∼1,327.60, US$ 26.14) and 1,603.09 pesos (CI: 1,259.07∼1,947.12, US$ 38.47) respectively for a vaccine with 70–80% and 90–100% efficacy; 294.94 pesos (CI: 161.38∼428.45, US$ 7.08) for a vaccine with 10 y of protection; 410.48 pesos (CI: 276.72∼544.24, US$ 9.85) and 501.74 pesos (CI: 366.73∼636.74, US$ 12.04) respectively for a vaccine with moderate and mild risk of side-effects; and 344.81 pesos (CI: 184.41∼505.20, US$ 8.28) for a single shot vaccine.

Non-leptospirosis case respondents also valued efficacy as the most important vaccine attributes. Compared to the base levels, they were willing to pay 732.53 pesos (CI: 611.99∼853.06, US$ 17.58) and 1,091.32 pesos (CI: 939.29∼1,243.34, US$ 26.19) respectively for a vaccine with 70–80% and 90–100% efficacy; 217.87 pesos (CI: 159.89∼239.01, US$ 5.74) and 231.09 pesos (CI: 166.15∼296.01, US$ 5.55) respectively for vaccine with 7 and 10 y of protection; 157.84 pesos (CI: 93.26∼222.42, US$ 3.79) and 181.23 pesos (CI: 117.65∼244.81; US$ 4.35)

Table 3. Estimates of implicit prices for each of the non-monetary attributes of the leptospirosis vaccine by case respondents

Vaccine Attribute		Leptospirosis Case Respondents [1]	Non-Leptospirosis Case Respondents [2]	Difference [1]–[2]
Base Level	**Improved Level**	**Implicit price[a] (95% C.I)**	**Implicit price[a] (95% C.I)**	**(| t | -Ratio)**
EFFICACY of 50–60%	EFFICACY of 70–80%	1,089.04***	732.53***	356.52***
		(850.49∼1,327.60)	(611.99∼853.06)	(26.34)
	EFFICACY of 90–100%	1,603.09***	1,091.32***	511.78***
		(1,259.07∼1,947.12)	(939.29∼1,243.34)	(32.16)
PROTECTION of 2 years	PROTECTION of 7 years	198.61	217.87***	−19.25
		(332.23∼65.00)	(153.69∼282.05)	(1.92)
	PROTECTION of 10 years	294.92***	231.09***	63.83***
		(161.38∼428.45)	(166.16∼296.01)	(6.34)
SERIOUS RISK of side-effects	MODERATE RISK of side-effects	410.48***	157.84**	252.65***
		(276.72∼544.24)	(93.26∼222.42)	(25.12)
	MILD RISK of side-effects	501.74***	181.23***	320.51***
		(366.73∼636.74)	(117.65∼244.81)	(31.84)
Given in 3 SHOTS	Given in 2 SHOTS	204.61	188.84	15.77
		(499.56∼−90.34)	(359.75∼17.93)	(1.02)
	Given in 1 SHOT	344.81***	239.01***	105.80***
		(184.41∼505.20)	(159.89∼318.12)	(9.57)

Notes: ***denotes statistical significance at 1% level and **5% significance; [a]In pesos (1 peso = US$ 0.024 based on October 2012 exchange rate).

respectively for a vaccine with moderate and mild risk of side-effects; and 239.01 pesos (CI: 159.89∼239.01, US$ 5.74) for a single shot vaccine.

Table 3 also shows the differences in the implicit prices of the 2 case respondents. Except for vaccine attributes related to protection of 7 y and 2 shots, the implicit prices of all other attributes derived for the leptospirosis case respondents were significantly higher at 1% level when compared with the derived values for the non-leptospirosis case respondents. Non-leptospirosis case respondents only exhibited a higher implicit price for leptospirosis vaccine with 7 y of protection, in which leptospirosis case respondents considered such attribute insignificant in their vaccination choice decision. The implicit prices for 2-shot leptospirosis vaccine were positive, but had no significant effect on their vaccination choice decision.

Willingness to pay (WTP) for combined attributes of leptospirosis vaccine

The respondents' willingness to pay for combined attributes of leptospirosis vaccine was estimated using compensating surplus model. **Table 4** presents the respondents' WTP for 2 vaccine scenarios containing an improved combination of vaccine attributes. For Scenario 1, leptospirosis and non-leptospirosis case respondents were willing to pay 1,903.88 pesos (CI: 1,413.35∼2,394.41, US$ 45.69) and 1,297.39 (CI: 1,057.35∼1,537.43, US$ 31.14) respectively for a leptospirosis vaccine with a combined attributes of 70–80% efficacy, 7 y of protection, mild risk of side-effects and if given in 2 shots. For Scenario 2, leptospirosis and non-leptospirosis case respondents were willing to pay 2,745.62 pesos (CI: 2,174.81∼3,316.43, US$ 65.89) and 1,743.19 pesos (CI: 1,504.74∼1,981.64, US$ 41.84) respectively for a leptospirosis vaccine with a combined attributes of 90–100% efficacy, 10 y of protection, mild risk of side-effects and if given in a single shot. The results also showed significant differences in the WTP values between the 2 case respondents at 1% level. Leptospirosis case respondents were willing to pay 600.49 and 1,002.43 pesos more for both vaccine scenarios than non-leptospirosis case respondents.

Discussion

Preferences for and implicit prices of leptospirosis vaccine attributes

We found that the acceptability of a hypothetical leptospirosis vaccine is influenced by the attributes of the vaccine. Respondents generally preferred leptospirosis vaccine with higher level of efficacy, longer duration of protection, mild to moderate risk of side-effects, given in single shot, and at a lower price. Our results are consistent with the reported responses for other vaccines in the literature, thereby providing evidence of face validity.[16,19,21]

Among the leptospirosis vaccine attributes, efficacy had the greatest impact on acceptability. Current leptospirosis vaccines with 70–100% efficacies are more likely to be accepted if introduced in the country. The higher implicit price for leptospirosis vaccine with 90–100% efficacy implies that further improving the vaccine efficacy from 70–80% to 90–100% will significantly increase its marginal value by 47–50%. Although respondents' have varied preferences for duration of protection attribute, such that non-leptospirosis case respondents preferred vaccine with 7 and 10 y of protection while leptospirosis case respondents only preferred 10 y of protection, our results still support the need to improve the current leptospirosis vaccines that are known to induce short-lived immunity.[9,10] Respondents were also willing to accept leptospirosis vaccine with mild to moderate risk of side-effects. However, their implicit prices for these attributes were lower compared to efficacy attributes levels, suggesting that respondents may be willing to accept and endure mild or moderate side-effects as long as higher efficacy is guaranteed. It is unlikely that future leptospirosis vaccine will be developed without any risk of side-effects. Therefore, post-surveillance of vaccine safety is important to identify any risk factors predisposing the development of any serious or adverse side-effects. This would entail ensuring that reporting system among local clinics or hospitals are in place, and providing support to health workers at the local community level to effectively monitor any consequential side-effects after vaccination.

Table 4. Estimates of respondents' willingness to pay (WTP) for combined attributes of leptospirosis vaccine

	Leptospirosis Case Respondents [1]	Non-Leptospirosis Case Respondents [2]	Difference [1]–[2]
Vaccine Attribute Combinations	WTP in pesos[a] (95% C.I.)	WTP in pesos[a] (95% C.I.)	($\|t\|$-Ratio)
Scenario 1: EFFICACY of 70–80% PROTECTION of 7 years MODERATE RISK of side-effects Given in 2 SHOTS	1,903.88 (1,413.35∼2,394.41)	1,297.39 (1,057.35∼1,537.43)	606.49*** (31.41)
Scenario 2: EFFICACY of 90–100% PROTECATION of 10 years MILD RISK of side-effects Given in 1 SHOT	2,745.62 (2,174∼3,316.43)	1,743.19 (1,504.74∼1,981.64)	1,002.43*** (49.33)

***denotes statistical significance at 1%; [a]1 peso = US$ 0.024 based on October 2012 exchange rate.

Our results showed that respondents only preferred single shot leptospirosis vaccine implying that current leptospirosis vaccines with 2 or more shots.[9,10] are less likely to be accepted if introduced in the country. A possible solution may include the use of social marketing campaigns for promoting public acceptance of future leptospirosis vaccine.[22] Such campaigns may highlight the efficacy and safety of leptospirosis vaccine in place of the number of vaccine shots. Additionally, improving the effectiveness of current leptospirosis vaccines by a single shot may also be considered by drawing from the experience learned in the development and delivery of single dose human papillomavirus (HPV) vaccine.[23,24]

Finally, we found that price was negatively associated with vaccine acceptance. This is consistent with the findings of Pennie et al.[25] indicating an increase in vaccination rates with low cost hepatitis B vaccine. Vaccine prices are reported to impede the implementation of vaccination program.[26,27] A higher vaccine price may limit access to the proportion of the population who cannot afford to pay, thereby reducing the effectiveness of vaccination campaigns. Options for effective mechanisms to lower leptospirosis vaccine prices may include the use of bulk purchasing and tiered pricing.[26,28] Possible integration of leptospirosis vaccination into the national immunization program may also be explored to capitalize on available human resources and health infrastructures that are already in place, thereby minimizing the cost of delivery. More recently, the medical cost of leptospirosis has been included in the benefit package of the Philippine Health Insurance, except for the cost of vaccination.[29] Perhaps the inclusion of leptospirosis vaccination in both public and private insurance packages may also be considered as an alternative financing mechanism.

Socio-demographics and leptospirosis vaccination acceptance

The interaction between socio-demographic variables and ASC in the model indicated that respondents' age, education, family size and income, proximity of homes to rivers and sewers, and leptospirosis awareness level significantly affected probability of accepting the leptospirosis vaccination program. The negative association between age and leptospirosis vaccination acceptance is consistent with the findings in the literature, indicating age-reluctance to pay for HPV and HIN1 influenza vaccinations.[30,31] The risk of acquiring leptospirosis infection is usually higher among younger individuals.[32,33] Perhaps younger respondents may perceive themselves at higher risk, and therefore more likely to accept leptospirosis vaccination. The positive association between education level and leptospirosis vaccination acceptance confirms findings from other studies, showing that higher education is correlated with the use of preventive health care services.[34,35] This result may be explained by the reason that more educated individuals usually have more knowledge about the true effect of inputs on their health, and are able to choose input allocations that produce better health outcomes than less educated individuals.[36,37] Considering that lower educational level is correlated to the risk of *Leptospira* infection,[38] continued health information education and communication (IEC) programs should be an integral component of future leptospirosis vaccine delivery. As supported by our results showing positive association between respondents' level of awareness and vaccination acceptance, IEC programs will be beneficial in raising public awareness of leptospirosis and in promoting positive attitudes toward vaccination.

The negative association between family size and leptospirosis vaccine acceptance is consistent with previous findings showing reduced vaccination uptakes with increased household size.[39,40] This result could possibly be explained by the dilution of resources associated with large family, which may exert a negative effect on the provision of preventive care to family members. The positive association between household income and leptospirosis vaccine acceptance reflects the findings of Weaver et al.[19] indicating an increase in HIV vaccine acceptability with increase in income. Considering that the incidence of leptospirosis is higher in low-income populations,[3,41,42] a community vaccination program wherein free or partially subsidized leptospirosis vaccines are provided to large and low income households may provide means to ensure equitable access to vaccine.

Living in proximity to a river can make individual highly vulnerable to flooding, which is pre-disposing factors for epidemics of leptospirosis.[42-46] Perhaps this could explain the positive association between proximity of respondents' homes to rivers and leptospirosis vaccination acceptance. Similarly, we expected a positive association between proximity of respondents' homes to a sewer and leptospirosis vaccine acceptance considering that sewers often serve as habitat for rats, hence a risk factor for leptospirosis transmission. Contrary to our expectation, our results showed that respondents living near to a sewer were less likely to accept leptospirosis vaccination. Recent study also found similar association showing that individuals living near to a sewer are less likely to contribute their time to leptospirosis prevention than those living far from a sewer.[47] Urban homes located near to sewers are inherently linked to urban slums and poverty.[48,49] Possibly, respondents living near to a sewer are facing extreme poverty, thereby refusing to accept leptospirosis vaccination. While subsidizing vaccination to impoverished areas may encourage uptake, it is also important that future leptospirosis vaccination program should be implemented along side with improving the health and sanitation conditions of urban slum communities. Focusing efforts on urban slum communities may significantly contribute to leptospirosis prevention program goals, since these communities account for about 37% of Metro Manila's population.[49]

WTP for combined attributes of leptospirosis vaccine

In our analysis, the estimated WTP of both case respondents for combined attributes of leptospirosis vaccine varied from 1,297.39 pesos to 2,745.62 pesos (US$ 31.14 – US$ 65.89). The estimated WTP values may be compared to the Japanese retail price of about 900 pesos to 1000 pesos (US$ 21.60-US$ 24.00) for polyvalent leptospirosis vaccine. Considering that the estimated WTP values exceed that of the Japanese leptospirosis vaccine retail price, our findings suggest a significant potential for introducing leptospirosis vaccine in the Philippine vaccine market. Noting further that the estimated WTP values represent

the maximum range of prices that respondents would agree to pay for leptospirosis vaccination, our results could serve as reference for vaccine manufacturers in their pricing decision, such that, if leptospirosis vaccine is introduced at price equal or less than their estimated WTP values, then individuals are more likely to buy the vaccine.

Our results also indicated that leptospirosis case respondents were willing to accept leptospirosis vaccination, and their estimated WTP values were significantly higher than non-leptospirosis case respondents. Personal experience on the burden of leptospirosis may have motivated leptospirosis cases respondents to place higher value on disease prevention. Hadisoemarto and Castro.[50] reported similar results indicating that individuals who had personal experience with dengue are twice more likely to accept dengue vaccination than those who did not have any personal dengue experience.

Limitations

We draw attention to some limitations of the study. First, our sample for leptospirosis case respondents contained a large proportion of male respondents, which may have inadvertently introduced sample bias. We attributed this to existence of gender differences in the manifestation of leptospirosis, wherein male gender is commonly cited as risk factor for infection.[4] Previous investigation of leptospirosis cases in Metro Manila also reported similar results indicating the predominance of male leptospirosis patients (90%) in the sample.[51] Second, we have selected the most important leptospirosis vaccine attributes through literature review, interviews and group discussions with medical experts in the field of leptospirosis vaccine research from Japan and Philippines; however these methods do not guarantee that we have included all vaccine attributes that are relevant to our respondents' preferences. Finally, respondents were presented with hypothetical vaccine scenarios. It is possible that their preferences may differ once actual leptospirosis vaccine will be available in the country. Nonetheless, our study provided us with useful insights on the relative importance of vaccine attributes to the respondents, the potential improvements on current leptospirosis vaccines, and the possible delivery strategies of future leptospirosis vaccine in the Philippines. Future research might consider comparing both stated and revealed preference approaches to measure vaccination uptake once leptospirosis vaccine is made publicly available in the country.

Conclusion

Our study is the first to estimate individuals' preferences for leptospirosis vaccine attribute and to quantify the value of combined leptospirosis vaccine features. Our findings have broader policy implications for future leptospirosis vaccine acceptability and dissemination. The high WTP estimates for leptospirosis vaccine may underscore the need for public or private investment toward the development and delivery of leptospirosis vaccine in the Philippines. Vaccine research efforts may focus on developing leptospirosis vaccine with higher efficacy, longer duration of protection, with mild to moderated risk of side-effects, given in single shot, and at a lower price, considering that these attributes all proved to influence individuals' preferences for vaccination. Preference heterogeneity across respondents with different sociodemographic characteristics may pose potential challenges to the acceptability of future leptospirosis vaccine. To ensure further acceptance and equitable access to future leptospirosis vaccine, public health authorities may consider the following vaccine delivery strategies: use of social marketing and education campaigns, provision of effective post-surveillance system for vaccine safety, use of bulk purchasing and tiered pricing, provision of free or partially subsidized vaccine during community vaccination program, inclusion of leptospirosis vaccination in national immunization program and insurance health packages, and inclusion of urban health and sanitation activities in the vaccination program.

Methods

Review of leptospirosis vaccines

The DCE design process began with a literature review on recent developments on human leptospirosis vaccines. Available literature have indicated that current human leptospirosis vaccines contain whole-cell of inactivated leptospires.[52] The monovalent vaccine from France contains an inactive strain of *Leptospira icterohaemorrhagiae*, and initially given in 3 shots followed by biannual revaccination.[7] The trivalent vaccine from Cuba contains serovars of C*anicola*, Copenhageni and Mozdok.[9] Vaccination is given in 2 shots at 6-week intervals. The polyvalent vaccine from Japan contains serovars of *Autralis*, *Autumnalis*, *Hebdomadis,* and *Copenhageni*.[10] It is given in 2 shots followed by a booster injection after 5 y.

The current leptospirosis vaccines are still facing major issues related to short-term and serovar-specific protection, including concerns on efficacy and safety with the use of inactivated whole-cell preparation.[53,54] Their duration of immunity varied from less than 2 y to a maximum of 7 y after vaccination, while their efficacies range from 60% to 100%.[7-10,55,56] The side-effects have been reported to include: mild local reactions such as skin redness, hard lump, swelling, local pain and itching; systemic reactions such as fever, headache, fainting, nausea and vomiting; and serious autoimmune disease like inflation of vascular structure of the eyes.[7,8,10,57] The use of recombinant, lipopolysaccharide and DNA-based vaccines may offer solutions to some of the limitations of current leptospirosis vaccine [53,54]. However, their applications are still in exploratory and may take years until new leptospirosis vaccines will be commercially available.

Identification of attributes, questionnaire design and administration

The attributes and levels used to describe leptospirosis vaccine were identified through literature review and subsequent discussions with medical professors ($n = 2$) who specialized in

leptospirosis vaccine research at Kyushu University, Japan and public health experts ($n = 5$) involved in the leptospirosis prevention and control (LEPCON) project in the Philippines. The attributes identified were efficacy, duration of protection, risk of side-effects, number of vaccine shots and price. These attribute levels were selected by considering their relevance to both clinical and policy viewpoint. Except for price attribute which contained 6 levels, the other 4 attributes contained 3 levels. The combinations of 4 vaccine attributes with 3 levels and one attribute with 6 levels ($3^4 \times 6^1$) resulted in 486 combinations of hypothetical vaccine profiles. For practical reasons, a total of 36 hypothetical leptospirosis vaccine profiles were constructed using orthogonal design obtained from the tables of orthogonal arrays.[58] The 36 leptospirosis vaccine profiles were taken as choice sets for vaccination program A. A fold-over technique with cyclical shifting of the vaccine profiles in program A was performed to derive vaccine profiles for program B.[59,60] A *no vaccination* option was added to allow respondents to *opt-out* (**Table S1**). The 36 choice sets were divided into 3 questionnaires to minimize non-response rate due to large number of choice sets. The questionnaire began with the assessment of the respondents' socio-demographic profiles, and questions about their awareness of leptospirosis. In the DCE section, the choice sets were presented and the respondents were asked to select their most preferred alternative. To facilitate better understanding of the choice scenarios, the questionnaire was translated in local language, researchers took extra time in describing the choice attributes, and a separate sheet containing description of vaccine attributes and levels was displayed as reference for the respondents (**Table S2**). All respondents were also given the opportunity to ask questions and to clarify information on all aspects of the research. The questionnaire was initially pretested prior to actual survey, which enabled us to check the clarity and easiness of the choice tasks, improved the description of the attributes and coherently arranged the socio-demographic questions. The questionnaire was included as part of the burden of leptospirosis study of the LEPCON program, which was approved by the Ethics Committee of the University of the Philippines-College of Public Health (UP-CPH).

The choice experiment was conducted from August to October 2012 across 30 *barangays*[1] in Metro Manila. These *barangays* were sampling sites of the previous burden of leptospirosis study of UP-CPH, and had an estimated leptospirosis prevalence of 32%.[6] The researchers interviewed a total of 342 households consisting of 114 index cases of diagnostically confirmed leptospirosis derived from UP-CPH, and 228 non-leptospirosis cases randomly selected from neighboring households. The non-leptospirosis case households were selected by skip interval method using the house location of the leptospirosis case household as the starting point. The eligible households included those who did not have any members previously diagnosed with leptospirosis. Within each eligible household, one adult (≥18 years old) respondent was selected using an alphabetical random selection procedure. All respondents were adequately informed about all aspects of the research, and gave their informed consent to participate in the study.

Analytical framework

The respondents' preferences for leptospirosis vaccine were analyzed using Random Parameters Logit (RPL) model to take in to account heterogeneity and avoid the independence of irrelevant alternative (IIA) violation caused by the introduction of the opt-out (option C) alternative in the choice set.[61,62] The random utility function with random parameters is given by:

$$U_{ij} = V_{ij} + \varepsilon_{ij} \equiv X_{ij}^{'}(\beta + \eta_i) + (Z_i^{'}\varphi)ASC + \varepsilon_{ij} \qquad (1)$$

where respondent i ($i = 1 \ldots N$) obtains utility U from choosing a leptospirosis vaccination program alternative $j(j = A, B, C)$ in the given choice set. The utility is composed of indirect utility function V and unobservable error term ε. The indirect utility component V is assumed to be a function of the vector of choice specific leptospirosis vaccine attributes X_{ij} with the mean coefficient of coefficients β; and the vector of interaction between the respondent's socio-demographic characteristics Z_i and alternative specific constant (ASC) with coefficients φ. Due to preference heterogeneity, β may vary across respondents in accordance to stochastic deviation η that captures respondent i preference relative to the average preference of the population. The probability of choosing a vaccination program alternative j in the choice set is derived by specifying the distribution of ε and β. The coefficients are estimated through simulated maximum likelihood based on n Halton draws from specified distribution. Choice probabilities are estimated by integrating the joint simulated distribution.[63]

In this study, the RPL model is composed of 3 indirect utility functions related to the 3 leptospirosis vaccination program options. The indirect utility function for *no vaccination* option C was set to zero, while the indirect utility functions for the 2 leptospirosis vaccination programs (A and B) followed a strictly additive form:

$$\begin{aligned} V = {} & \mathrm{ASC} + \beta_1 \mathrm{EFFICACY70\_80} + \beta_2 \mathrm{EFFICACY90\_100} \\ & + \beta_3 \mathrm{PROTECTION7} \\ & + \beta_4 \mathrm{PROTECTION10} + \beta_5 \mathrm{MODERATERISK} \\ & + \beta_6 \mathrm{MILDRISK} + \beta_7 \mathrm{2SHOTS} \\ & + \beta_8 \mathrm{1SHOT} + \beta_9 \mathrm{PRICE} + \varphi_1 \mathrm{AGE} * \mathrm{ASC} \\ & + \varphi_2 \mathrm{EDUCATION} * \mathrm{ASC} \\ & + \varphi_3 \mathrm{FAMILYSIZE} * \mathrm{ASC} + \varphi_4 \mathrm{INCOME} * \mathrm{ASC} \\ & + \varphi_5 \mathrm{MALE} * \mathrm{ASC} \\ & + \varphi_3 \mathrm{FAMILYSIZE} * \mathrm{ASC} + \varphi_4 \mathrm{INCOME} * \mathrm{ASC} \\ & + \varphi_5 \mathrm{MALE} * \mathrm{ASC} \\ & + \varphi_6 \mathrm{MARKET} * \mathrm{ASC} + \varphi_7 \mathrm{RIVER} * \mathrm{ASC} + \varphi_8 \mathrm{SEWER} * \mathrm{ASC} \\ & + \varphi_9 \mathrm{AWARENESS} * \mathrm{ASC} \end{aligned} \qquad (2)$$

[1]The term *barangay* represents the lowest geopolitical subdivision in the Philippines

where $\beta_1 - \beta_9$ are coefficients of the vaccine attributes; $\varphi_1 - \varphi_9$ are coefficients of the interaction terms between the Alternative Specific Constant (ASC) and socio-demographic characteristics of the respondents. Since the DCE includes an *opt-out* option, the ASC was equaled to 1 for leptospirosis vaccination program A and B, and 0 for *no vaccination* option C.[62] The interaction terms revealed which respondents' characteristics affect the likelihood of accepting the 2 leptospirosis vaccination programs against the *no vaccination* option. All non-monetary vaccine attribute levels were effects coded (**Table S3**) to avoid confounding effects with the opt-out option.[64] Except for price, all vaccine attributes were set as random parameters with normal distribution. The price attribute was set as non-random variable for reasons of identification and stability.[61] The distribution simulations were based on 500 Halton draws using NLOGIT 4 software.[62,65] The RPL model for leptospirosis and non-leptospirosis case respondents were separately estimated under the assumption that the 2 respondents differ in their vaccination preferences. To test this heterogeneity, the parameter estimates from the separate models were compared with the pooled model containing the observations of both case respondents using the log-likelihood (*LL*) ratio test:[66]

$$-2(LL_{pooled\ model}) - (LL_{Leptospirosis\ cases} + LL_{Non-leptospirosis\ cases}) \quad (3)$$

The implicit prices are used to express the marginal willingness to pay for a change in one vaccine attribute level in the choice set.[67] For effects-coded vaccine attribute k with 3 levels ($L = l1, l2, l3$), the implicit price for each attribute level of interest was calculated using equation 4: [68,69]

$$\text{Implicit Price}_{kL} = -\frac{\beta_{kL} - (-\beta_{kl1})}{\beta_p} \quad (4)$$

where β_{kL} is coefficient of the attribute level of interest; β_p is the coefficient of price attribute; and β_{kl1} is the coefficient of the base attribute levels, which is equivalent to the negative sum of the coefficients of the other 2 levels ($l2, l3$) in the model.[20,70] The base levels included the following attributes: efficacy of 50–60%, protection of 2 years, serious risk of side-effects, and 3-shot vaccine. The 95% confidence intervals for the implicit prices were estimated using the delta method implemented from the Wald command in NLOGIT. The implicit price estimates may also represent a rescaled coefficient which can be used for model comparison across treatments.[64] Hence, the differences on the implicit price estimates between leptospirosis and non-leptospirosis case respondents were assessed using t-test statistics at 5% level of significance.

Respondents' willingness to pay (WTP) for combined features of leptospirosis vaccine attributes can be estimated using the compensating surplus model. The compensating surplus shows the change in income that would make a respondent indifferent between the base-case and subsequent alternative scenarios with specified combination of vaccine attributes. Estimates of compensating surplus (CS) were calculated using equation 5: [70]

$$\text{CS} = -\frac{1}{\beta_m}(V_o - V_1) \quad (5)$$

where β_m is the marginal utility of income assumed to be equal to the coefficient of the price attribute; V_o represents the utility of the base-case scenario; and V_1 represents the utility of an alternative vaccine scenario.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Supplemental Material

Supplemental data for this article can be accessed on the publisher's website.

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