

1 CONSUMER WILLINGNESS TO PAY FOR DENGUE VACCINE (CYD-TDV, 2 DENGVAXIA®) IN BRAZIL; IMPLICATIONS FOR FUTURE PRICING 3 CONSIDERATIONS

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37 38 **Abstract**

39
40 Introduction and objective: Dengue virus is a serious global health problem with an
41 estimated 3.97 billion people at risk for infection worldwide. In December 2015, the
42 first vaccine (CYD-TDV) for dengue prevention was approved in Brazil, developed by
43 Sanofi Pasteur. However, given that the vaccine will potentially be paid via the public
44 health system, information is need regarding consumers' willingness to pay for the
45 dengue vaccine in the country as well as discussions related to the possible inclusion of
46 this vaccine into the public health system. This was the objective of this research.
47 Methods: We conducted a cross-sectional study with residents of Greater Belo
48 Horizonte, Minas Gerais, about their willingness to pay for the CYD-TDV vaccine.

1 Results: 507 individuals were interviewed. These were mostly female (62.4%) had
2 completed high school (62.17%), were working (74.4%), had private health insurance
3 (64.5%) and did not have dengue (67.4%). The maximum median value of consumers'
4 willingness to pay for CYD-TDV vaccine is US\$33.61 (120.00BRL) for the complete
5 schedule and US\$11.20 (40.00BRL) per dose. At the price determined by the Brazil's
6 regulatory chamber of pharmaceutical products market (CMED) for the
7 commercialization of Dengvaxia[®] for three doses, only 17% of the population expressed
8 willingness to pay for this vaccine. Conclusion: Brazil is currently one of the largest
9 markets for dengue vaccine and the price established is a key issue. We believe the
10 manufacturer should assess the possibility of lower prices to reach a larger audience
11 among the Brazilian population.

12
13 Keywords: Dengue, Willingness to pay, Vaccine, Consumers, Brazil

14 15 **1. Introduction**

16
17 Dengue is an arbovirolosis transmitted to humans by the bite of a mosquito of the *Aedes*
18 genus, especially, *Aedes aegypti*. It is estimated that 390 million infections occur
19 annually worldwide (Gubler, 2011; Bhatt *et al.*, 2013), with the number of cases of
20 dengue increasing in frequency and geographic region (Guzman *et al.*, 2010; Brady *et*
21 *al.*, 2012; Simmons *et al.*, 2012; Bhatt *et al.*, 2013). Based on mathematical modelling,
22 the global annual incidence has been estimated at approximately 50 to 100 million
23 symptomatic cases each year in recent years (Beatty *et al.*, 2011; Bhatt *et al.*, 2013).
24 This flavivirus represents an important social and economic impact in most tropical and
25 subtropical countries, and it is currently estimated that approximately US\$5million are
26 spent annually on hospitalizations related to dengue worldwide (Suaya *et al.*, 2009).
27 However, this is now likely to be a considerable under-estimate.

28
29 Dengue is endemic in Brazil, with a high and increasing incidence in recent years
30 (Brasil, 2011; Brasil, 2013; Brasil, 2016). In 2015, there were 1,587,080 registered
31 cases probably due to dengue, 839 deaths and an incidence of 782.6 cases /100,000
32 inhabitants. In the State of Minas Gerais, there was a demonstrated incidence of 879.8
33 cases/100,000 inhabitants and 67 deaths (Brasil, 2016). Data released by the National
34 Information System of Notifiable Diseases (SINAN) demonstrated the occurrence of
35 2,320,956 and 4,406,767 cases of dengue in the state of Minas Gerais and Brazil
36 respectively between 2010 to 2014 (Brasil, 2014a). In 2014, more than 150 million
37 Brazilian reais (US\$42.016million) were spent on surveillance, prevention and control
38 of dengue and chikungunya virus in Brazil (Brasil, 2014b).

39
40 Until now, there has not been a specific licensed treatment for dengue, and the
41 development of effective vaccines against all four serotypes of DENV is an important
42 strategy to control this flavivirus and significantly contribute to reducing the disease
43 burden (Webster *et al.*, 2009; Durbin *et al.*, 2011). Common strategies to help control
44 dengue include preventing mosquitoes from accessing egg-larving habitats, using
45 environmental management interventions such as removing artificial man-made
46 mosquito habitats, emptying and cleaning domestic water storage containers, as well as
47 personal and household protection including applying insecticides (WHO, 2016).
48

1 Recently, the tetravalent chimeric vaccine CYD-TDV from Sanofi Pasteur was
2 approved for the prevention of dengue in endemic countries including Mexico, the
3 Philippines, El Salvador, Costa Rica, Paraguay and Brazil (Brasil, 2015; DVI, 2015;
4 Roland *et al.*, 2015). The disappointing results in individuals under 9 years of age
5 (Hadinegoro *et al.*, 2015) led to vaccine being indicated for the population 9 years or
6 older. The resultant approved indication from this first dengue vaccine is for individuals
7 9 to 45 years (e.g. Brazil) or 9 to 60 years of age (e.g. Paraguay), depending on the
8 license (WHO, 2016).

9
10 CYD-TDV was evaluated during the active phase of surveillance (25 months post-
11 enrolment) in CYD14 (Capeding *et al.*, 2014) and CYD15 (Villar *et al.*, 2015). As per
12 the protocol, vaccine efficacy against virologically-confirmed symptomatic dengue
13 illness was 56.5% (95% CI; 43.8% - 66.4%) in CYD14, assessed in Asia, and CYD15
14 with 60.8% (95% CI; 52% - 68%) evaluated in clinical trials conducted in Latin
15 America including Brazil. Sanofi Pasteur recommended the administration of three
16 doses each six months apart (WHO, 2016). However, the complete duration of vaccine
17 protection is still unknown (HADINEGORO *et al.*, 2015; WHO, 2016).

18
19 The Brazil's regulatory chamber of the pharmaceutical products market (CMED) is
20 responsible for evaluating and establishing the prices of medicines for
21 commercialization in Brazil by Resolution n°2 of 5 March 2004, referencing prices for
22 the same medicines in other countries including Australia, Canada and the United States
23 (Brasil, 2004). From prices established by CMED, pharmaceutical companies may
24 apply for incorporation of their products into the national health system by sending a
25 process submission to the National Commission on Technology Incorporation of the
26 National Health System (CONITEC) (Brasil, 2008). In this context, endemic countries,
27 including e Brazil, will have to make important decisions such as the possible
28 incorporation of this vaccine into their public systems within a context of constrained
29 budgets. In this scenario, pharmaco-economic evaluations, such as the assessment of
30 willingness-to-pay and cost-effectiveness analysis, are important for decision-making
31 (Palanca-Tam, 2008; Lee *et al.*, 2015).

32
33 Willingness-to-pay (WTP) is a relevant methodological approach to estimate the
34 maximum amount that an individual is willing to allocate to programs, services and
35 health technologies. It is usually applied in cost-benefit analysis and in health
36 technology assessment (Haab and McConnell, 2002). The lack of available WTP studies
37 with the Brazilian consumer for a dengue vaccine, and the possible upcoming
38 vaccination with CYD-TDV in the country, is a concern given the potential budget
39 impact and the current economy situation. This study sought to estimate the Brazilian
40 consumers' willingness to pay for this vaccine in order to contribute to the debate and
41 pharmaco-economic reviews focusing on demand and potential prices for dengue
42 treatments in Brazil.

43 44 **2. Material and Methods**

45
46 This study estimated the willingness to pay of Brazilian consumers towards the CYD-
47 TDV dengue vaccine through an analysis of contingent valuation, which enables
48 evaluation of the monetary amount an individual is willing to pay to acquire a certain

1 product or service using questionnaires with direct questions. The respondents did not
2 have the disease at the time of the interview, but they may or may not have had dengue
3 in the past (Haab and McConnell, 2002).

4 5 **2.1 Design and study location**

6 The survey was conducted in the metropolitan region of Belo Horizonte, capital of
7 Minas Gerais State, the second most populous state in Brazil. Minas Gerais state has
8 21,013,869 inhabitants with 2,375,151 inhabitants currently registered in the Belo
9 Horizonte metropolitan region. In addition, Belo Horizonte and Brazil presented,
10 respectively, a mean Human Developed Index of 0.810 and 0.737 in 2010 (Atlas do
11 Desenvolvimento Humano, 2016).

12
13 Minas Gerais State is similar to Brazil as a whole for certain aspects including mean
14 income per capita and socio demographics. Mean income per capita was US\$315.97
15 (1128.00BRL) for Brazil and US\$311.76 (1113.00BRL) per month for Minas Gerais in
16 2015 (IBGE, 2014; Agencia Brasil, 2016). In addition, despite that there being 26 States
17 in the country, Minas Gerais has one sixth of the Brazilian cities and represents a
18 relevant epidemiological context for the flavivirus (BRASIL, 2014a; 2016). In addition
19 in 2013, Minas Gerais was the State with the highest number of dengue cases in the
20 country (Brasil, 2014a). Consequently, providing a robust sample for the study.

21
22 Participants were interviewed using a questionnaire developed by the research team,
23 based on a literature review (Haab and McConnell, 2002; Palanca-Tam, 2008; Lee *et al.*,
24 2015). The survey was conducted in May 2016 and the interviews were undertaken by
25 graduate and undergraduate students of the Faculty of Pharmacy of the Federal
26 University of Minas Gerais, trained to conduct interviews and answer possible
27 questions.

28 29 **2.2 Data collection instrument**

30 The technique for measuring the willingness to pay is the application of a questionnaire,
31 with prior presentation to the respondent of all the features of the disease and the
32 intervention necessary for decision-making, as well as the involved conditions and
33 important aspects of the clinical context of the disease. To fully implement this
34 technique, it is essential that all participants have received the same information. This
35 was assured by specific and intensive training of the interviewers (Haab and McConnell,
36 2002).

37
38 The questionnaire was divided in five sections: (1) Questions to understand what the
39 participants knew about dengue; (2) Information about the disease, intervention and
40 alternatives for disease prevention; (3) Questions to test the understanding of the
41 information provided; and (4) Discrete Choice, Bidding Game and Open-Ended
42 questions (Haab and McConnell, 2002). Section 5 consisted of a self-reported
43 socioeconomic questionnaire. The questions in section (4) were included in order to
44 assess whether individuals would be willing to pay US\$54.05 (180.00 BRL) for the
45 three-dose scheme of CYD-TDV vaccine as well as obtain an estimate of a range of
46 values and a point estimate that respondents would pay for the technology.

47

1 US\$54.05 for three doses of CYD-TDV for the Discrete Choice technique was
2 established based on the maximum price for the consumer of the yellow fever vaccine -
3 US\$19.50 (64.92BRL) (Fiocruz Laboratory), established by CMED in 20 July 2016
4 (Anvisa, 2016).

5
6 All questions related to the research context and/or difficulties in completing the
7 socioeconomic questionnaire were clarified by the interviewers. The information about
8 the mean effective protection for all four serotypes (approximately 60%), as well as the
9 possibility of local (e.g. swelling at the site of application and pain) and systemic (e.g.
10 fever, myalgia, asthenia and headache) adverse events were included in the text read to
11 all participants in the initial stage of the interview. There was also a figure explaining
12 graphically the efficacy of the vaccine to aid the dissemination of information.

13 14 **2.3 Sampling and selection criteria**

15 Interview selection was random. Passers by in major circulation paths, close to parks,
16 markets and fairs in the metropolitan region of Belo Horizonte were invited to
17 participate and, if they agreed, answered the questionnaire in the same location.
18 Considering the scenario with higher uncertainty that is 50% respondents agreeing to
19 pay the value of US\$54.05 (180.00BRL), with a two-sided 0.05 significance, we
20 calculated a minimum of 400 respondents would be required in this research. .

21
22 Individuals could or not have history of dengue, but could not presently have symptoms
23 or have a diagnosis of the disease at the time of the interview. To be selected,
24 individuals must have declared that they have an income. Individuals under 18 without
25 their own income were excluded. In addition, participants who showed willingness to
26 pay higher than twice the value of their declared monthly income and individuals who
27 would not use this vaccine, even if it would be free, were excluded from the analysis in
28 line with previous publications (Lee *et al.*, 2015).

29 30 **2.4 Data analysis**

31 The willingness to pay for dengue vaccine was estimated by the median of the
32 maximum declared value by the individuals who were willing to pay any amount
33 greater than or equal to zero. The median among groups defined by covariates were
34 compared using the Mann-Whitney test (two groups) or Kruskal-Wallis test (three or
35 more groups). The significance level was 5%. All socioeconomic variables were
36 evaluated and the relation with the maximum value of willingness to pay for CYD-
37 TDV, such as education and income were included. To assess income variation, we
38 stratified the value of "<3"; "3-10" and "> 10" times the minimum wage, in order to
39 measure the percentage of individuals for each range.

40
41 Furthermore, we measured the frequency of the participants that have or not private
42 health insurance. According to the National Regulatory Agency for Private Health
43 Insurance and Plans (ANS), that regulates the private health insurances in Brazil, Minas
44 Gerais has a coverage of private health insurance of between 20% and 30%, with
45 5,467,559 beneficiaries in the State in 2014. The coverage in Brazil was 25.2% of the
46 population (48,824,150 individuals) in March 2016 (ANS, 2016a; b).

47

1 In addition, we further evaluated the relation of willingness to pay by individuals that
2 had previously had or not dengue. Statistical analysis was performed using Microsoft
3 Excel 2007, R (R CORE TEAM, 2014) and Minitab 17. For comparison purposes, we
4 adopted the conversion value established by the World Bank for Purchasing Power
5 Parities (PPPs) (2015: 1 US\$ = 3.330BRL).

6 7 ***2.5 Ethical considerations***

8 All interviews were conducted after reading and signing the Term of Free and Clarified
9 Consent. All researchers of the project signed a confidentiality agreement prior to the
10 interviews. This study was approved by the Ethics Committee of the Federal University
11 of Minas Gerais (COEP) under the CAAE 57219816.0.0000.5149.

12 13 **3. Results**

14 15 ***3.1 Population characteristics***

16 We conducted 507 interviews with individuals aged between 18 and 84 years old who
17 agreed to participate and answer the questionnaire. The mean age of respondents was
18 34.6 ± 12.8 years, 37.6% were male, 74.4% were working at the time of interview, and
19 37.8% had completed higher education (Table 1).

20
21 The participants who reported a history of dengue were 32.6%, the utilization of public
22 health service was reported by 49.3%, and those respondents who reported at least one
23 dengue case in the household were 43.8%. In approximately 70% of respondents, their
24 family income was below five times the minimum wage (Table 1).

1 Table 1. Characteristics of the respondents

2	Variable	n	(%)**
	Age in years [mean (SD)]	34.6	12.5%
	Men	188	37.6%
	Has children	197	(38.9%)
	Educational level		
	Had never attended school	2	0.4%
	Complete primary education	46	9.3%
	Completed high school	261	52.5%
	Complete college or more	188	37.8%
	Currently working	372	74.4%
	Have health insurance	318	64.5%
	Dengue history	162	32.6%
	Had dengue and reported having used only the public health system	68	49.3%
	Had dengue and reported having used only a private health provider	54	39.1%
	Had dengue and reported have used both services	16	11.6%
	Reported that other people in the household had dengue	212	43.8%
	Family income (number of minimal wages)*		
	<1		8.5%
	1-2		15.4%
	2-3		15.2%
	3-5		20.7%
	5-10		22.5%
	10-20		7.9%
	>20		1.2%

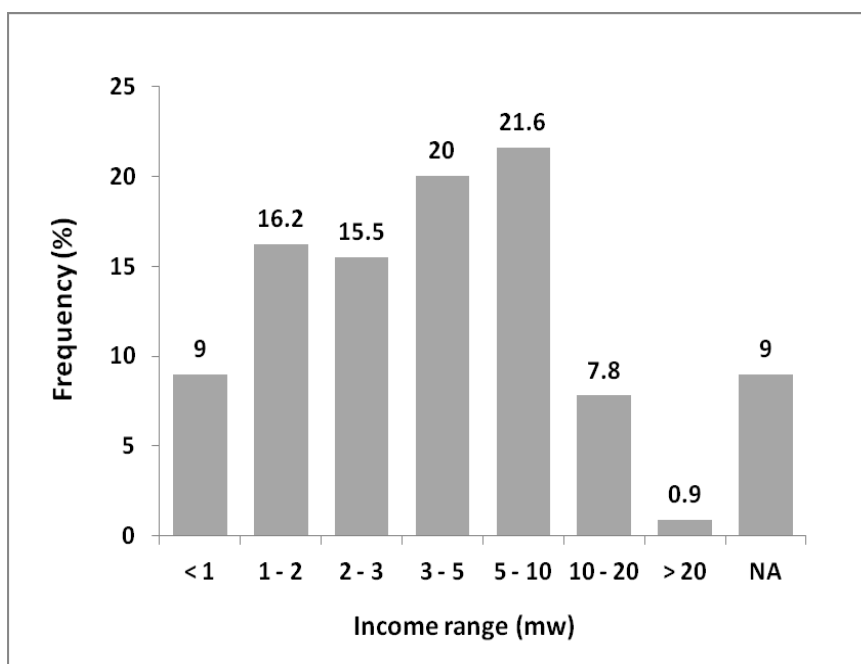
3 *Notes: * 8.6% of respondents refused to answer on family income. **The value of the difference to reach*
4 *100% in all questions, are due to answers such as "I do not know" and "I do not want to answer".*

5 6 **3.2 Willingness to pay for CYD-TDV dengue vaccine**

7 Of the 507 subjects, 7.3% said they would not be vaccinated even if CYD-TDV did not
8 have any cost. The main reasons for this were efficacy (37.8%) and safety (40.5%). In
9 addition, only three (8.1%) respondents said they did not use any vaccines and fifty-nine
10 (11.6%) said they would use this vaccine only if it would be provided free of charge.
11 Considering these exclusions criteria, 464 respondents were eligible for the WTP
12 analysis.

13
14 Among these 464 individuals, 37.9% were men, 88.8% had completed high school or
15 more, 39.2% had children, 73.7% were working at the moment of interview, 62.1% had
16 health insurance and 31.7% had previously had dengue. The participants who reported a
17 family income up to 10 times the minimal wage were 83.4% (Figure 1).
18

1 Figure 1. Family income of respondents included in analysis of the willingness to pay
 2 for dengue vaccine (Dengvaxia®) in this study

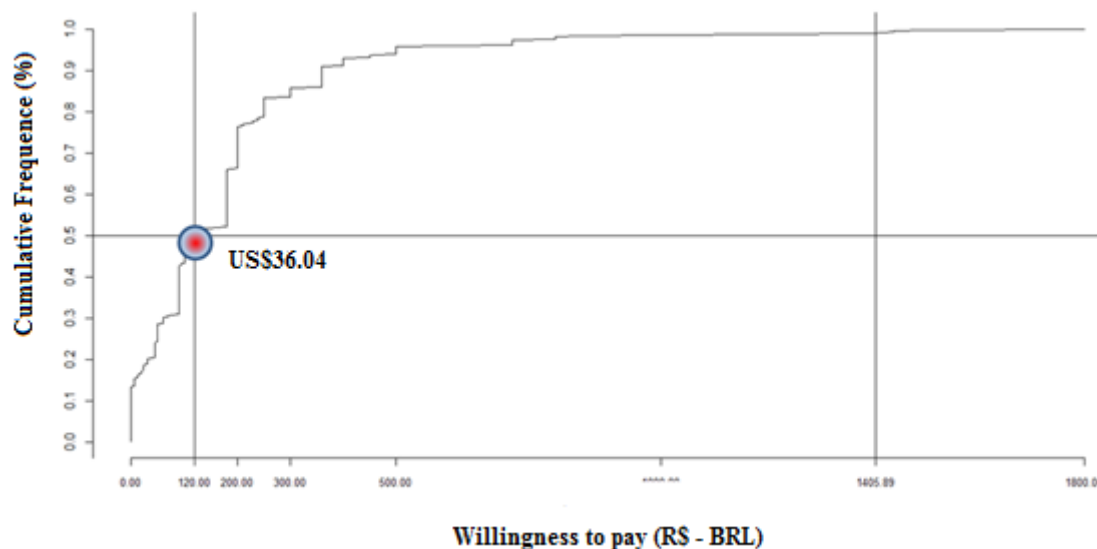


3
 4 * NA: Not available - The respondents that answered, "I do not know and I do not want to answer";
 5 mw = minimal wage

6 With the application of the Discrete Choice Technique, it was found that 44% of
 7 participants were willing to pay US\$54.05 (180.00BRL) for the three-dose regimen of
 8 the vaccine. Of the 190 respondents who had children, 131 (68.9%) were willing to pay
 9 USD\$54.05 for CYD-TDV vaccination of their family. Results of the Bidding Game
 10 technique revealed that, in general, the amount the respondents were willing to pay
 11 ranged from US\$27.03 (90.00BRL) to US\$108.11 (360.00BRL), representing 54.1% of
 12 individuals involved in interview. The minimum and maximum willingness to pay for
 13 three doses of CYD-TDV vaccine were of 0.00 and 1,800.00 BRL.

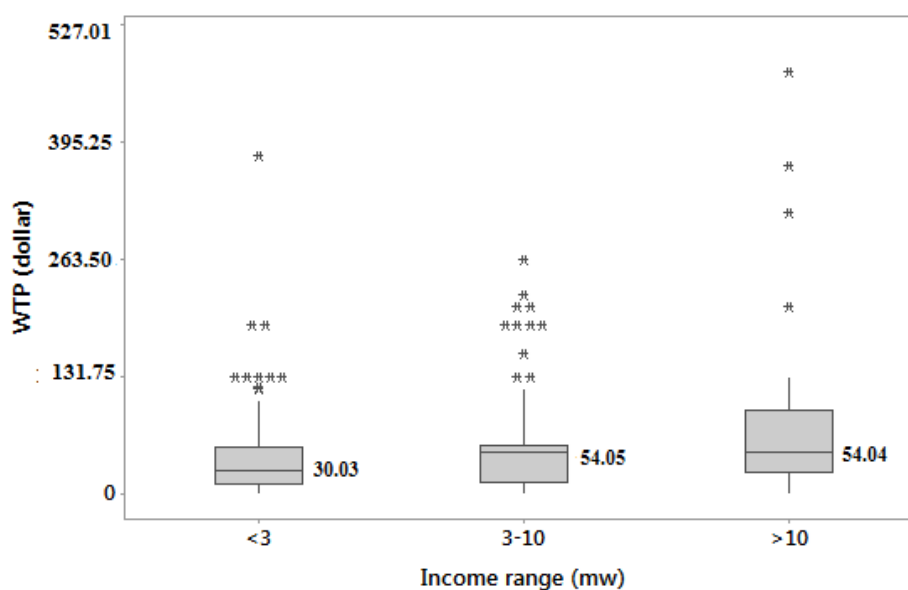
14
 15 The willingness to pay for dengue vaccine by the Brazilian consumer was estimated at
 16 the median value of US\$36.04 (120.00BRL) for the three-dose regimen or US\$12.01
 17 (40.00BRL) per dose. This means that 50% of individuals interviewed reported
 18 maximum values of willingness to pay equal to or less than US\$36.04 (Figure 2).
 19
 20
 21
 22
 23
 24
 25

- 1 Figure 2. Cumulative percentage of individuals willing to pay for CYD-TDV vaccine
 2 according to the maximum values reported



- 3
 4 The only variable correlated with willingness to pay with statistical significance (<0.05)
 5 was monthly income ($p = 0.003$) when stratified as "<3", "3-10" and "> 10" times the
 6 minimum wage, representing family income values under US\$739.50 (2,640.00BRL)
 7 (30.8%), between US\$792.79 (2,640.00BRL) and US\$2,642.64 (8,800.00BRL) (34.1%)
 8 and above US\$2,642.64 (6.9%), respectively, per month. Median values of willingness
 9 to pay for these three groups were respectively US\$30.03 (100.00BRL) and US\$54.05
 10 (180.00BRL) for the highest income groups (Figure 3). As expected, the increase of
 11 family income contributed to a higher willingness to pay, which is logical and
 12 consistent with the published theory (Haab and McConnell, 2002).
 13

1 Figure 3. Box plot of the willingness to pay for three doses of CYD-TDV according to
2 family income.



3
4 NB. The results were statistically significant (< 0.05); (*) Extreme values presented for each income
5 range; mw = minimal wage
6
7

8 Discussion

9
10 This study sought to estimate the willingness to pay among Brazilian consumers for the
11 dengue vaccine recently licensed in the country, with the study population having
12 similarities with the profile of the Brazilian population as a whole. This included certain
13 characteristics such as higher percentage of women (51.4%), a low percentage of
14 individuals who have never studied (8.5%) and the percentage of individuals with at
15 least 11 years of education (41.8%) (IBGE, 2014). The percentage of families in our
16 study with income less than 5 times the minimum wage was just under 70% (Table 1).
17 This value was below the Brazilian Institute of Geography and Statistics (IBGE) in their
18 profiling family in the national context, where the percentage was 87.9%. This might
19 contribute for a higher median value of willingness to pay for the vaccine compared to
20 the national population (IBGE, 2014).
21

22 In this study, the percentage of respondents who reported having health insurance was
23 64.5% (ANS, 2016b). The Brazilian private market for health insurance is strictly
24 regulated by the National Regulatory Agency for Private Health Insurance and Plans,
25 which works on behalf of the Ministry of Health. Private health insurance can either be
26 purchased individually or obtained as a work benefit, depending on the employer. The
27 Brazilians that decide to purchase private health insurance may still access public health
28 services if they wish or need. The Brazilian public health system, named SUS, was
29 established in 1988 by constitution in order to guarantee access to health care to the
30 entire population. The public system maintains primary and outpatient centers,
31 hospitals, diagnostic laboratories and should provide access to pharmaceuticals
32 including vaccines (Rizzotto and Campos, 2016).

1
2 The median willingness to pay value for CYD-TDV was US\$33.61 (120.00/11.20BRL
3 dose) for the three-dose scheme and clinical efficacy of 60% (Hadinegoro *et al.*, 2015;
4 Godói *et al.*, 2016). The reason for expressing values in medians in willingness to pay
5 analysis (Palanca-Tam, 2008; Hadisoemato *et al.*, 2013; Lee *et al.*, 2015) is that the
6 mean is sensitive to outliers, which may contribute to an erroneous perception of what
7 the population is indeed willing to pay. The median value of US\$33.61 shows the
8 maximum amount 50% of respondents would be willing to pay; however, this does not
9 represent an estimated average number of people willing to pay for the vaccine
10 (Buckland *et al.*, 1999).

11
12 This study is the first study in Brazil to consider the actual scenario of a possible
13 vaccination with CYD-TDV with clinical information arising from clinical phase III
14 trials (Capeding *et al.*, 2014; Villar *et al.*, 2015) and from the 25 months follow-up
15 study (Hadinegoro *et al.*, 2015). Other studies adopted a hypothetical vaccination
16 scenario with 100% safety and efficacy and with protection for 10 years and for life, as
17 seen, respectively, in the studies conducted in the Philippines (Palanca-Tam, 2008) and
18 Indonesia (Hadisoemato *et al.*, 2013). However, we believe this is an unrealistic
19 scenario given the current clinical information.

20
21 The number of doses used in the studies was also variable. A single dose study was
22 conducted in the Philippines (PALANCA-TAM, 2008) and Indonesia (Hadisoemato *et al.*
23 *et al.*, 2013) and three doses in Vietnam, Thailand and Colombia (Lee *et al.*, 2015), which
24 is similar to our study. Among the respondents in our study, 7.3% reported not wishing
25 to be vaccinated even if the vaccine was free of charge. The same situation happened in
26 the studies from Vietnam, Thailand and Colombia (Lee *et al.*, 2015).

27
28 The willingness to pay of Brazilian consumers of US\$33.61 (BRL120.00) is closer to
29 that observed in endemic countries such as Vietnam and Colombia. This is between the
30 values found in Vietnam at US\$26.13 and the Philippines at US\$60.00. The observed
31 values in Indonesia, Colombia and Thailand and were respectively US\$ 1.94, US\$22.60
32 and US\$ 69.78. The studies published in the context of willingness to pay for dengue, in
33 general, considered a hypothetical dengue vaccine with results of efficacy, safety and
34 protection time better than the results seen with CYD-TDV in phase III clinical trials
35 (Palanca-Tam, 2008; Hadisoemato *et al.*, 2013; Lee *et al.*, 2015). Consequently, again
36 questioning the findings.

37
38 The Brazil's regulatory chamber of pharmaceutical products market is an inter-
39 ministerial body responsible for price setting. New-patented innovative products such as
40 Dengvaxia[®] are classified as Class I. As a result, manufacturer prices may not exceed
41 the lowest price in the following markets: Australia, Canada, France, Greece, Italy, New
42 Zealand, Portugal, Spain or United States of America (Brasil, 2004). However since
43 CYD-TDV is not marketed in these countries, CMED had no comparison to establish a
44 price for vaccine in Brazil. On July 25th of 2016, CMED reported that the manufacturer
45 price for each Dengvaxia[®] dose in Brazil may vary from US\$37.19 to US\$38.80
46 (132.76 to 138.53BRL) according to the States (provinces) tax rates of each of the 26
47 states of Brazil. For Minas Gerais State, the maximum consumer price is US\$37.71
48 (134.63BRL). Considering the need for three doses of the vaccine to achieve planned

1 efficacy, the amount paid for each person vaccinated will be at least US\$113.13
2 (403.89BRL), which represents the willingness to pay of only 17% of the population in
3 this study.

4
5 Mahoney et al (2012) studying the production costs of another dengue vaccine, which is
6 being developed at the Butantan Institute, found that the production scale (15 million
7 doses per year) in ten vials should cost around US\$0.51 to US\$0.65 per vial. When the
8 quantity produced increases to 60 million doses per year, the cost of production could
9 potentially fall to US\$0.20 per dose. The authors demonstrated that vaccines for
10 Japanese encephalitis and type A meningitis are available in developing countries at
11 prices below US\$1.00 per dose. This is much lower than consumer prices demanded by
12 manufacturer in Brazil or established by CMED.

13
14 Brazil has a comprehensive immunization program with coverage for an appreciable
15 number of infections. In future scenarios, we believe public health systems purchasing
16 the dengue vaccine should assess carefully the cost-effectiveness ratio in combination
17 with a budget impact analysis, as the efficacy of this new dengue vaccine may be
18 considered insufficient compared to other vaccines for similar conditions or disease
19 burden with appreciably lower prices. Comparisons with other vaccines prices and
20 effectiveness for diseases with similar burden may contribute to political decisions
21 regarding the possibility of incorporating this technology into public health systems at
22 acceptable and reasonable prices, bearing in mind the current economic climate in
23 Brazil and the desire to continue to offer universal healthcare. Such discussions have
24 grown in recent times driven by the increasing prices for new medicines especially new
25 cancer medicines and those for orphan diseases, despite costs of research and
26 production estimated at US\$50 to 100 million per compound by some authors (Experts
27 in Chronic Myeloid Leukemia, 2013; Godman *et al* 2015; Howard *et al.*, 2015; Tefferi
28 *et al.*, 2015; Phelan *et al.*, 2014; Bruijin *et al.*, 2016).

29
30 In a study conducted in Brazil, Araújo et al (2016) estimated the potential impact of
31 vaccination against dengue. In a more conservative scenario, the authors estimated a
32 22% reduction in cases of dengue (routinely vaccinate up to 9 years old and vaccination
33 campaign up to 10 years) and 81% in the liberal scenario (routine to 9 years and
34 vaccination campaign up to 40 years) over 5 years. Furthermore, they demonstrated that
35 vaccination could reduce 233,000 hospitalizations due to the disease during the
36 considered period. CYD-TDV was licensed for individuals with age between 9 and 45
37 years old (Brasil, 2015a). However, it is important to balance this against the potential
38 budget impact. This especially as it is important to emphasize that all efforts and
39 strategies for vector control by governments and society will need to continue since the
40 vaccine has only 60% efficacy, and especially because of other existing arboviruses,
41 such as Chikungunya and Zika, with Zika related to microcephaly epidemics in Brazil
42 (Brasil, 2015b).

43
44 The contingent valuation is the most common approach to estimate the monetary value
45 for goods and services from hypothetical questions (Haab and McConnell, 2002;
46 Palanca-Tam, 2008; Hadisoemato et al., 2013; Lee et al., 2015). However, some
47 limitations are noted such as the respondents may not have full information (e.g.
48 disease, severity and frequency of symptoms) or that it may simulate a scenario very

1 distinct and different compared with the real situation (e.g. efficacy of the intervention).
2 To avoid such limitations, the questionnaire used must be complete and up to date and
3 include all relevant situations and conditions related to the intervention or service in the
4 analysis to avoid possible bias (Boyle, 2003). This study was conducted using efficacy
5 results extracted from the analysis of 27,355 individuals from 2 to 16 years old
6 (Hadinegoro *et al.*, 2015). These results was used to grant commercial license to
7 Dengvaxia[®] for children as well as adults in Brazil and in other countries (Godói *et al.*,
8 2016). Consequently, helping to address such concerns. Real-world results of the
9 vaccine are currently missing, which may overestimate the value of the WTP (if
10 effectiveness is lower), or underestimate the value (if effectiveness is higher – most
11 unlikely scenario). In addition, the respondent's willingness to pay were constrained
12 within the attributes and levels presented in this study. Lastly, the random sample used
13 may not be fully generalizable to population of Brazil as a whole. However despite
14 these limitations, we believe our findings do provide guidance to the Brazilian
15 authorities and the manufacturers of the vaccine on potential pricing and reimbursement
16 strategies.

17
18 In conclusion, despite the limitations regarding income differences between citizens in
19 Minas Gerais and Brazil as a whole as well as limitations with the sampling method, we
20 believe this study provides important information about how much consumers are
21 willing to pay for the CYD-TDV vaccine approved in Brazil to avoid the risk of being
22 infected. From the price determined by CMED for commercialization of Dengvaxia[®]
23 (Minas Gerais) i.e. US\$113.13 for three doses, only 17% of the participants involved in
24 this study were willing to pay for this vaccine, and this from a higher income base than
25 Brazil as a whole. This is a concern given the current resource constrained environment
26 in Brazil. We believe based on our study findings, that the manufacturers may wish to
27 reconsider their pricing strategy. This is because Brazil constitutes one of the largest
28 markets for dengue vaccine and there are appreciable competing demands on available
29 resources, especially given the current economic situation in Brazil.

31 **Conflict of Interest Statement:**

32 The authors declare that the research was conducted in the absence of any commercial
33 or financial relationships that could be construed as a potential conflict of interest.

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