

## CONSUMER WILLINGNESS TO PAY FOR A HYPOTHETICAL ZIKA VACCINE IN BRAZIL AND THE IMPLICATIONS

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### ABSTRACT

Background: Zika virus is a newly emerging infection, associated with increasingly large outbreaks especially in tropical countries such as Brazil. A future Zika vaccine can contribute to decreasing the number of cases and associated complications. Information about consumers' willingness to pay (WTP) for a hypothetical Zika vaccine can help price setting discussions in the future in Brazil, starting with the private market. Methods: A cross-sectional study conducted among residents of Minas Gerais, Brazil, regarding their WTP for a hypothetical Zika Vaccine. The mean effective protection was 80%, with the possibility of some local and systemic side-effects. Results: 517 people were interviewed. However, 30 would not be vaccinated even if the vaccine was free. Most of the resultant interviewees (489) were female (58.2%), had completed high school (49.7%), were employed (71.2%), had private health insurance (52.7%) and did not have Zika (96.9%). The median individual maximum willingness to pay for this hypothetical Zika vaccine (one dose) was US\$31.34 (BRL100.00). Conclusion: Such discussions can contribute to decision-making about prices once a Zika vaccine becomes available in Brazil alongside other ongoing programmes to control the virus.

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### 1. INTRODUCTION

The Zika virus is a newly emerging infection associated with increasingly large outbreaks. In the most recent outbreak in Brazil, an estimated 326,224 cases were confirmed between May 2015 and March 2018 [1-3]. Zika is an arbovirolosis transmitted to humans by the bite of a mosquito of

the *Aedes* genus such as *Aedes africanus*, *luteocephalus*, *vittatus*, *furcifer*, *picoargenteus*, *hensilli*, *albopictus*, with the most important vector in Brazil being *Aedes aegypti* [4]. This latter vector is associated with other transmissions such as dengue, chikungunya, and the yellow fever virus [5]. The common symptoms associated with Zika are headache, conjunctivitis, fever, erythema, myalgia, arthralgia retro-orbital pain, anorexia, vomiting, diarrhea, and abdominal pain. The symptoms usually last for 4 to 7 days and are typically self-limiting. However in severe cases, symptoms can include neurological disorders and neonatal malformations (microcephaly) [4].

The virus is a member of the *Flaviviridae* family and *Flavivirus* genus [6], and was isolated for the first time in 1947 from a sample of blood of a Rhesus Monkey in the Zika forest located in Uganda [7]. It was first isolated in humans in 1952 (Uganda, Tanzania), and in 1968 the virus was detected in humans in Nigeria [4].

The first substantial outbreak of Zika fever occurred in 2007 in Yap State (Western Pacific Ocean) with 185 suspected, 49 confirmed, and 59 probable cases of Zika virus infection. Before 2007, this virus was distributed widely in Africa and Asia [8]. In French Polynesia (October 2013) around 10,000 cases were registered, with approximately 70 severe cases, including neurological (Guillain Barré syndrome, meningoencephalitis) or autoimmune (thrombocytopenic purpura, leukopenia) complications [4]. These severe cases (neurological complications) can be associated with previous infections with other flaviviruses, especially the dengue virus [4]. The Asian genotype of this virus was responsible for a large epidemic in the Pacific Ocean islands between 2013 and 2014 as well as in 2015. This same genotype was associated with epidemics verified in 2015 in the American continent including Brazil [5].

According to World Health Organization (WHO), Zika virus epidemics are considered a serious health problem in the international context considering the appreciable increase in cases in recent years [4]. Since 2013, this virus has infected more than 1 million people in Latin America and the Caribbean [5].

The Zika virus infection was reported in Brazil for the first time in May 2015, and the largest incidence were registered in the Northeast and Middle-West Regions [1,2]. Additionally, in the Southwest Region, Minas Gerais State had 14,327 cases of this infection up till December 2017, demonstrating the impact of Zika virus in this region [2]. Between 2015 and 2017, there were 3017 confirmed microcephaly cases associated with Zika infection in Brazil. 65.3% (2004 cases) occurred in the Northeast region and 19.0% (542 cases) in the Southeast region, with 98 cases in Minas Gerais State [9]. 326,224 cases of this infection were confirmed over the country between May 2015 and March 2018 [1-3]. US\$4.649 billion was spent on dealing with Zika infection in a recent epidemic in Brazil between 2015 and 2017 (0.09% of the Brazilian GDP) [10].

There is currently no licensed treatment to eliminate the Zika infection [5]. The Brazilian government has implemented social mobilization programmes across a number of years to try and control as well as eliminate the vector in the country, especially during the summer [11]. Preventing mosquitoes from accessing egg-larving habitats using environmental management techniques such as cleaning domestic water storage containers and household protection (e.g. insecticides) are just some of the commonly used strategies to control the *Aedes* mosquitoes [11,12].

Vaccination is an approach that can induce protective immunity against the corresponding infectious agent. There are a several vaccines approved for infections such as cholera, hepatitis, Japanese encephalitis, yellow fever and rabies [13]. However, there are important diseases without a licensed vaccine including Chagas disease (American trypanosomiasis), Chikungunya, Zika, Cytomegalovirus, HIV and malaria. This reinforces the necessity to invest financial resources to develop new therapies (drugs or vaccines) for relevant clinical conditions in endemic countries [14].

The development of an effective vaccine against the Zika virus will represent an important strategy for the control of this infectious disease. However, currently there are no vaccines available for the Zika virus infection. Several companies and research groups have spent the

last years developing various types of vaccines in different stages of development [15]. The vaccine DNA ZIKV GLS-5700, developed by GeneOne Life Science/INOVIO Pharmaceuticals, has demonstrated an absence of serious adverse effects after administration in their Phase I clinical studies. Another vaccine is being developed by the Gene One Life Science/INOVIO Pharmaceuticals after it obtained positive results in relation to its safety during early Phase studies involved 40 participants [16]. The vaccine developed by the National Institute of Allergy and Infectious Diseases (NIAID) is currently in a clinical study involving 90 adults in the United States, and it is currently the most advanced candidate in the development for a Zika vaccine [17]. This vaccine induced mild to moderate adverse effects and exceeded the protective thresholds seen in animal studies [18]. Groups from FIOCRUZ, Butantan Institute and the Evandro Chagas Institute in Brazil are also researching a viable vaccine [19].

In Brazil, the Brazil's Regulatory Chamber of the Pharmaceutical Products Market (CMED) is responsible for determining the prices of medicines for commercialization in the country especially the private market. As part of this, CMED researches prices granted for medicines in other countries including Australia, Canada, France, Greece, Italy, New Zealand, Portugal, Spain, and USA, to help establish possible prices in Brazil. Any vaccine for Zika will be seen as a new product, and would be classified as Category I. This means that the manufacturer's price cannot exceed the lowest price for the same product in the selected countries. Pharmaceutical companies that intend to submit a new product to the Chamber's evaluation must prepare an Informative Document with appreciable information about the new medicine including, if is available, any economic evaluation incorporating any willingness to pay (WTP) studies [20].

WTP is a relevant economic evaluation to estimate the maximum amount that an individual is willing to allocate to services and health technologies. It is usually applied to quantify the value associated with a particular benefit (from the consumption of a technology or from a service) [21]. In Brazil, any economic assessment analyzing a health technology can contribute to discussions about the potential pricing of new medicines that will be evaluated by CMED, especially where these medicines are unlikely to be used or launched among the reference priced countries. This is likely to be the case with any new Zika vaccine approved in Brazil. Such WTP studies can also help in decision-making regarding incorporating any new technology into the Brazilian public health system (SUS) [22]. We are aware that there are a number of publications discussing WTP for infectious diseases [22 – 34]. However, we believe our study is the first study in Brazil to apply this to the Zika infection.

The Brazilian public health system (SUS) was established in 1990 based on decentralized universal access, with municipalities providing comprehensive and free health care to each individual in their locality [35,36]. Individuals may also decide to purchase private health insurance to obtain greater convenience and faster services which are not always available for those who use SUS services. However, the Brazilians who decide to purchase private insurance may still access public services if they need or want to [36]. Having said this, Dengue, Zika, Yellow Fever, and Chikungunya, are diseases with mandatory notification to the Brazilian Notifiable Diseases Information System (SINAN) and the first step for health care for these infections is usually in the public health system [37]. According to SINAN, the Middle-West, North, and Northeast regions of Brazil were responsible for the highest incidences of Zika cases in the country during 2017 at 39.3, 12.4 and 9.3 cases/100,000 habitants, respectively, compared with 4.3 cases/100,000 habitants in the Southeast region. In addition, the number of microcephaly cases were 2,004 in the Northeast and 584 in the Southeast region between 2015 and 2017 [1,2].

Endemic countries will have to make important decisions within the context of constrained budgets [38,39]. Pharmacoeconomics evaluations including cost effectiveness analyses are another type of methodology to help with decision-making [38,39] alongside willingness-to-pay studies [22], when allocating scarce resources.

Consequently, the aim of this study was to estimate the willingness to pay (WTP) among Brazilian consumers for a hypothetical Zika vaccine. We believe this is the first study involving consumers' willingness to pay for a Zika vaccine in Brazil to help with future debates focusing on potential prices for a Zika vaccine once this becomes available. This builds on our previous study examining such issues for a vaccine for dengue fever [22].

## 2. MATERIALS AND METHODS

This study estimated the willingness to pay (WTP) of Brazilian consumers for a hypothetical Zika vaccine via questionnaires. This included estimating the maximum value applied for a service or product that will bring benefit to patient's health in a hypothetical scenario [21,39]. Currently, no Zika vaccine is approved in any endemic country, and there is currently no study where the efficacy of a potential vaccine has been fully evaluated. Our study considered the price of US\$ 56.41 (180.00 BRL) per vaccination (single dose) as this figure was utilized in a previous study of willingness to pay for the first dengue vaccine approved by the private market in Brazil [22], and is similar to the price for the yellow fever vaccine marketed in some regions of Brazil [40]. Yellow fever and dengue virus are other important flaviviruses endemic in Brazil [5].

The respondents did not have this infection at the moment of the interview, but they may or may not have had Zika in the past, similar to previous studies in this area [22, 39].

### **2.1 Design and Study Location**

The survey was conducted in the metropolitan region of Belo Horizonte, capital of Minas Gerais State. This state has 21,013,869 inhabitants with 2,375,151 inhabitants registered in the Belo Horizonte metropolitan region. In addition, Belo Horizonte and Brazil presented 0.810 and 0.737, respectively, of a mean Human Developed Index [41].

The Brazilian and Minas Gerais State population have economic and socio demographic similarities. The mean gross monthly income per capita was US\$315.97 for Brazil and US\$311.76 for Minas Gerais in 2015 [42].

The respondents were interviewed using a questionnaire developed by the research group in accordance with other published studies [22,23,39]. The survey was conducted during the months of June and July 2017 by graduate and undergraduate pharmacy students of the School of Pharmacy of the Federal University of Minas Gerais. The students involved in this study received training prior to undertaking any interviews.

### **2.2 Data Collection Instrument**

The methodology to estimate the willingness to pay involved the application of a questionnaire [22,24,43] (Supplementary Material) that included the presentation to the respondent of all the features of the disease, clinical aspects about Zika virus infection, and the technology associated with decision-making. The interviewers were trained and all respondents received the same information. All doubts and any misunderstandings associated with the disease for this study were clarified before starting any interview [39].

The questionnaire was divided in five sections [43]. These included (i) Questions to understand what the respondents knew about Zika and information about clinical aspects and strategies for Zika prevention; (ii) Questions to evaluate the understanding of the information provided; (iii) Discrete Choice and Bidding Game questions; (iv) Open-Ended questions; and (v) a self-reported socioeconomic questionnaire [24,39]. In section 3, respondents were asked a discrete choice question about their willingness to pay US\$ 56.41 (180,00 BRL) for a hypothetical Zika vaccine (single dose). In section 4, we included questions involving higher or lower values compared with US\$56.41 associated with their willingness to pay for this hypothetical vaccine (Bidding Game) (Supplementary Material). At the end of this section, the participants were asked an open-ended question about the maximum value associated with their willingness to pay.

The hypothetical Zika vaccine had a mean effective protection for Zika virus of 80%, and the possibility of local events such as swelling and pain at the site of application and systemic side-effects including fever and headache. All events were included in the questionnaire. In addition, we utilized figures to explain graphically the protective effect of this hypothetical vaccine to help with interviewees' understanding.

### **2.3 Sampling and Selection Criteria**

Passersby in major circulation paths, markets, and fairs, in the greater Belo Horizonte region were randomly selected. The participation of the respondents was voluntary. The sample size calculation was based on the proportion of respondents agreeing to pay US\$ 56.11, with a margin of error 0.05 in a 95% confidence interval, considering the scenario with higher uncertainty, when this percentage would be around 0.5. In this situation, the size is calculated as  $1/(0.05^2) = 400$  respondents. We selected individuals who did not currently have Zika at the moment of the interview, who declared having an income and aged  $\geq 18$  years old. The respondents who demonstrated the willingness to pay higher than twice the value of their declared monthly income, or would not use this hypothetical vaccine even if it were free, were excluded from the analysis in line with previous publications [21-23].

### **2.4 Data Analysis**

We estimated the median of the WTP values only between the respondents who were willing to pay an amount greater or equal to zero. Consequently, the respondents who would not get the vaccine even for free were eliminated. The median values are usually used in willingness to pay analysis to reduce the influence of lower and higher values obtained during data collection (outliers) [21]. The Mann-Whitney test (two groups) or the Kruskal-Wallis test (three or more groups) was applied to compare the median values among the groups defined by covariates (significance level was 5%). The income declared was stratified in "<1-2", "2-5" and "5->20 times the minimum wage in order to measure the percentage of individuals for each range. The frequency of each group was evaluated together with the frequency of the respondents who have or not private insurance.

The statistical analyses were performed using Microsoft Excel 2007 and Mini Tab17. We applied for the conversion value determined by the Organization for Economic Co-operation and Development for Purchasing Power Parities (PPPs) of 2017: 1 US\$ = 3.191BRL [44].

### **2.5 Ethics**

All respondents interviewed were those who accepted to participate in the interview after reading and signing the Terms of Free and Clarified Consent. The information provided by the individuals is confidential and all researchers of this study signed a confidentiality agreement prior to the interviews. The study was approved by the Ethics Committee of the Federal University of Minas Gerais (COEP) under the CAAE 66860617.8.0000.5149.

## **3 RESULTS**

### **3.1 Characteristics of the population**

The study was conducted among 517 individuals aged between 18 and 91 years old, who agreed to answer the questionnaire. The mean age of respondents was  $38 \pm 14$  years, 58.2% were women, 71.2% were employed at the time of the interview and 49.7% had completed higher education (Table 1). 12.5% of the respondents who reported they had health insurance and had Zika history had used SUS services to treat this infection.

**Table 1: Characteristics of the Respondents (N=517).**

<b>Variable</b>	<b>N</b>	<b>%</b>
Age in years [mean (SD)]	38	(14)
Women	301	58.2
Has Children	251	48.5
Education Level		
Had never attended school	3	0.6
Complete primary education	101	19.7
Completed high school	255	49.7
Complete college or more	153	30.0
Currently working	368	71.2
Have health insurance	272	52.7
Had Zika	16	3.10
Reported that other people in the household had Zika	22	4.3
<b>Health service utilized by people who had Zika (N=16)</b>		
Private	8	50.0
Public	5	31.3
Both	1	6.3
Not Answered	2	12.5
<b>Family income (number of minimal wages*)</b>		
<1	43	8.3
1 to 2	100	19.3
2 to 3	105	20.3
3 to 5	102	19.7
5 to 10	102	19.7
10 to 20	22	4.3
>20	3	0.6
Not Answered	40	7.8

\*Brazilian Minimal Wage in 2017 = 937.00BRL (US\$293.63)

The respondents who had Zika history were 3.1%, and 31.3% had used the public health services for Zika treatment. In 59% of those interviewed, their family income was between 1 and 5 times the minimum wage (Table 1).

### **3.2 Willingness to Pay for a Hypothetical Zika vaccine**

Among the 517 interviewed, 30 (5.8%) would not be vaccinated even if the vaccine was available free of charge. The main reasons for this refusal were efficacy (30.0%), not using vaccines (36.7%) and safety (26.7%). Considering these exclusion criteria, 489 interviewed were eligible for the analysis of willingness to pay.

Among the 489 respondents, 58.4% were women, 79.2% had been at high school, 50.0% had children, 72.2% were employed, 56.8% had health insurance and 3.4% had Zika. Most of those interviewed had household incomes above twice the minimum wage (69.8%).

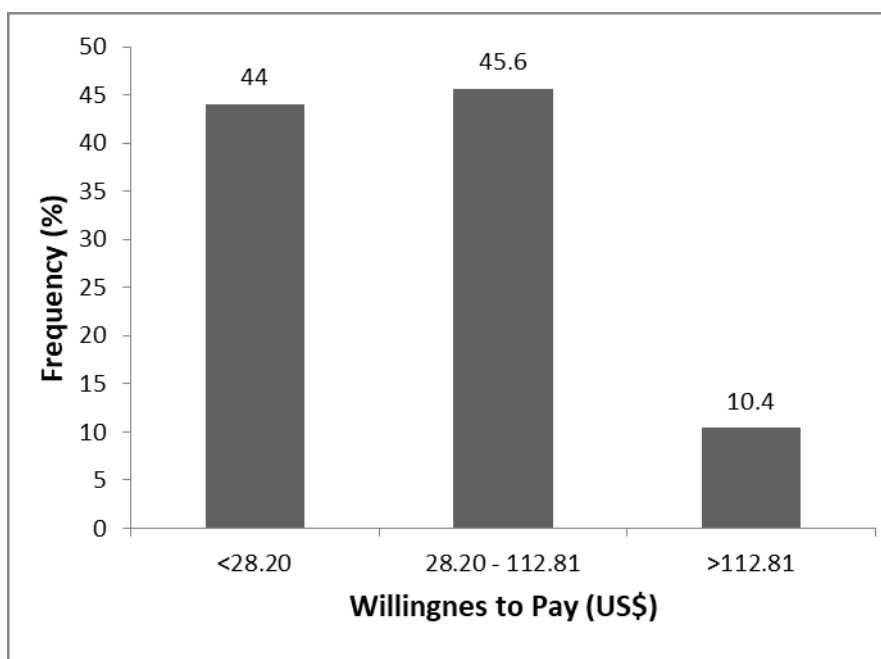
From the Discrete Choice Technique, 44.5% of respondents were willing to pay US\$ 56.41(180.00BRL) for a single dose of this vaccine. Among the 242 individuals who had children, 203 (83.9%) were willing to pay the same value to vaccinate their family. The Bidding Game Technique demonstrated that the value associated with the willingness to pay of 236 interviewed (45.66%) ranged between US\$ 28.20 (90.00 BRL) to US\$ 112.82 (360.00 BRL) (Figure 1). The minimum and maximum values reported were of \$0.00 and US\$ 902.54 (2880.00 BRL), respectively.

The median estimated value applied to the WTP for a hypothetical Zika vaccine by the Brazilian consumer was US\$ 31.34 (100.00BRL) (Figure 2).

The comparison tests between the WTP medians showed a significant difference between income classes ( $p = 0.000$ ) and people who have and do not have health insurance. When we stratified the income as “<1-2”, “2-5” and “5- >20” times the minimal wage, the frequencies were, respectively, 30.2% (<954.00BRL – 1908.00BRL), 43.5% (1908.01BRL – 4770.00BRL) and 26.3% (4770,01BRL - >19080BRL) (Figure 3 and 4).

When comparing the respondents' household income with the WTP responses, it is noted that the groups with higher incomes are willing to pay a higher value than those with lower incomes. 50% of people with a family income less than a minimum wage, and up to two times the minimum wage, were willing to pay an amount equal to or less than US\$ 18.80 (60.00BRL), while in the group with the highest income, 50% of individuals were willing to pay an amount equal to or below \$ 56.41(180.00BRL).

People who had health insurance showed a greater willingness to pay for the hypothetical vaccine than those who do not at USD 56.41(180.00BRL). No significant differences were found when comparing the values of WTP with variables of age, gender, education level, work and children.



**Figure 1: Range of maximum values of the willingness to pay (US\$) for a hypothetical Zika vaccine.**

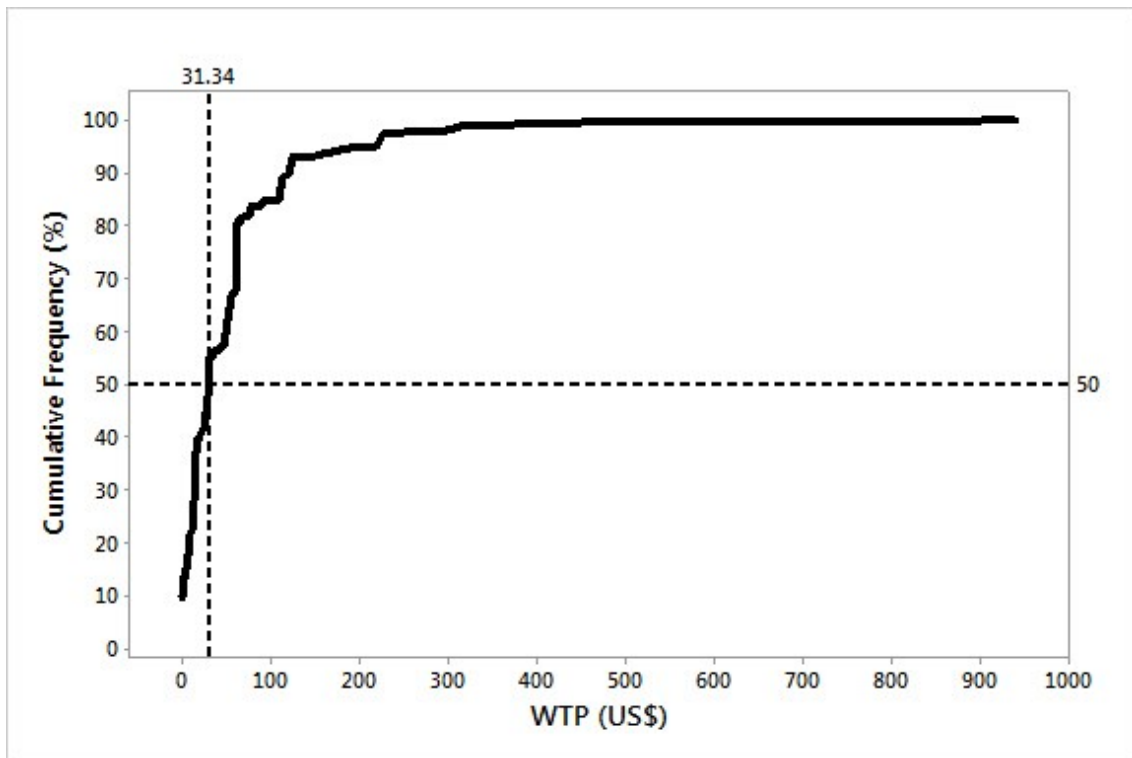


Figure 2: Cumulative percentage of the consumer willingness to pay (US\$) for a hypothetical Zika vaccine according to the maximum values reported.

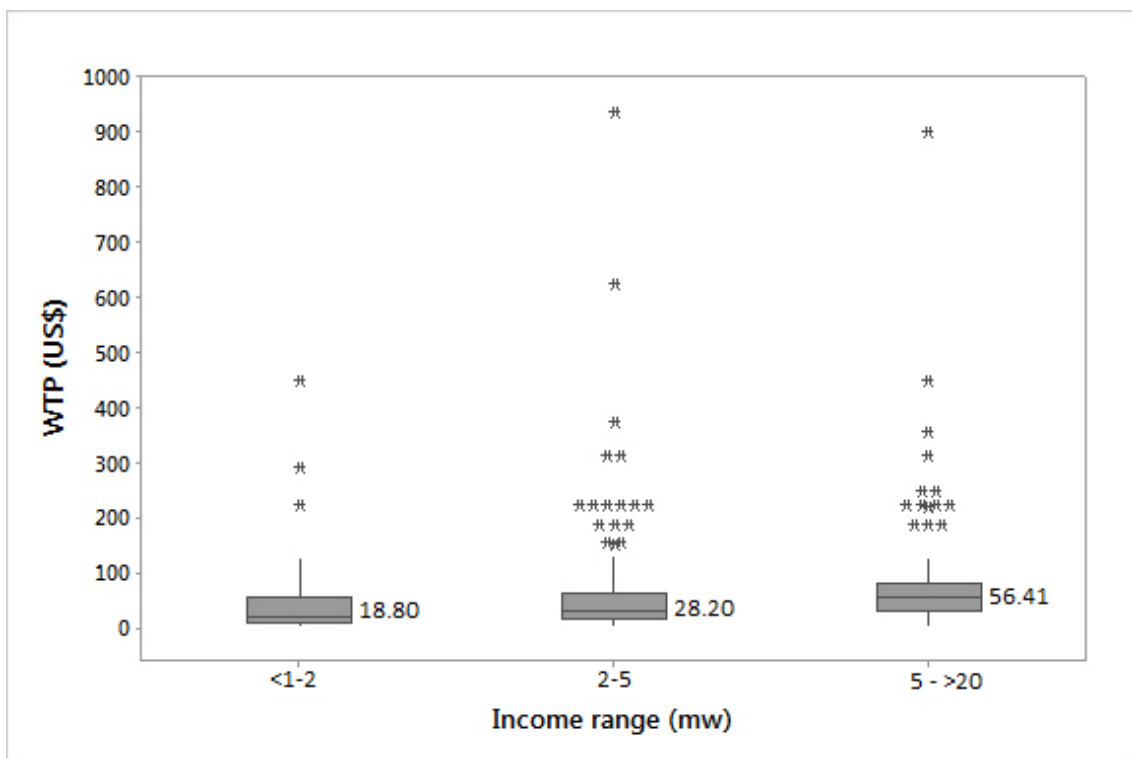
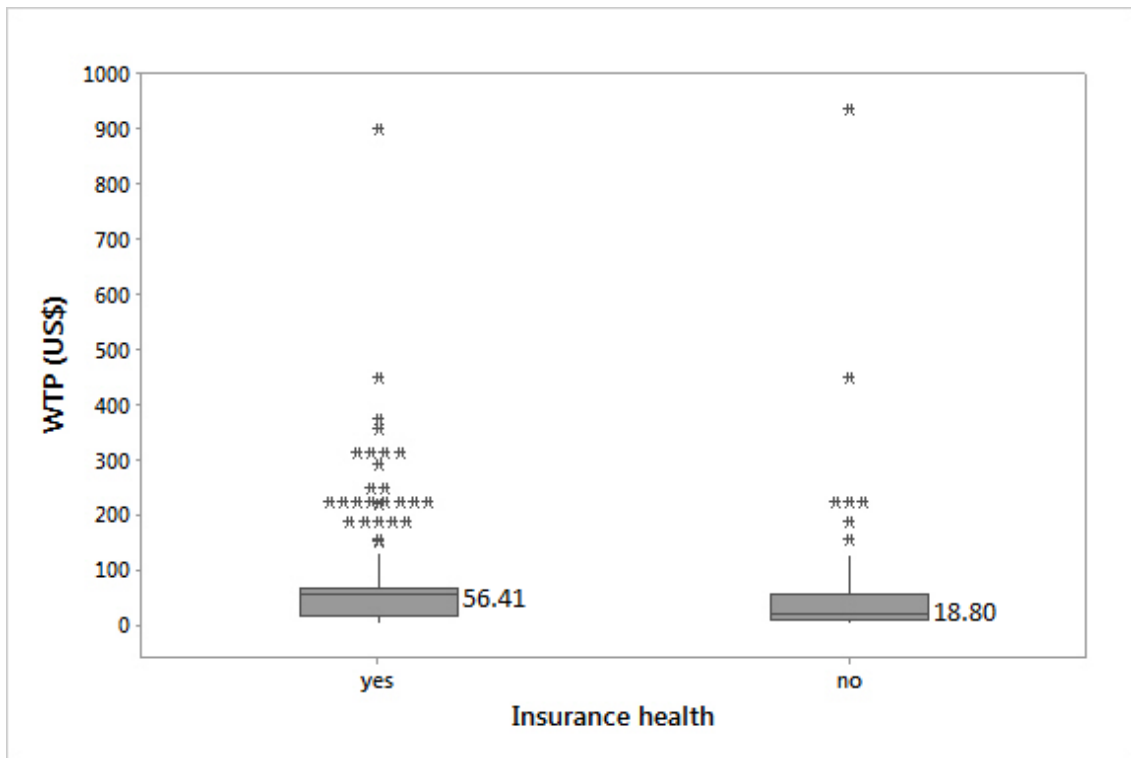


Figure 3: Box plot of willing to pay (US\$) for a hypothetical Zika vaccine according to the income range (highlighted values correspond to median WTP).





**Figure 4: Box plot of willing to pay for a hypothetical Zika vaccine according to the health insurance (highlighted values correspond to WTP medians).**

#### 4. DISCUSSION

Our study sought to assess the willingness to pay of the Brazilian consumers for a hypothetical Zika vaccine with efficacy of 80% to prevent this infection to help guide decision making in CMED when a new vaccine is launched.

Our study showed that the median of the maximum values of willingness to pay for a hypothetical Zika vaccine (single dose) with an efficacy of 80% was US\$ 31.34 (100.00BRL). On top of this, even when Brazil has the first Zika vaccine approved and funded, the authorities will need to continue with prevention services against the vector in view of the possibility to infect patients with other arboviruses, with 29.9% of our respondents not currently undertaking activities to eliminate the *Aedes* mosquitoes.

We did not find significant differences comparing the maximum valued applied to WTP for this hypothetical vaccine with age and gender. However perhaps not surprisingly, people with a higher family income and with health insurance are willing to pay more for the vaccine than those who have lower purchasing power (Figures 3 and 4). Consequently, for commercial success in countries such as Brazil, where most people are low-income earners, companies should be cautious about pricing vaccines for the Zika virus because even if it is a serious infection, people with low incomes would not buy the vaccine if the price was too high [42].

The median value associated with the WTP for this hypothetical Zika vaccine at US\$ 31.34 was lower though than US\$ 33.61 (120.00BRL) for the first dengue vaccine (Dengvaxia®) approved in Brazil in a previous study conducted to estimate the WTP for this vaccine among Brazilian consumers [22]. Considering the higher number of dengue cases (547,068) compared with zika cases (14,794) in 2016 in Minas Gerais state [45], we believe the greater prevalence can be associated with a higher WTP for dengue vaccination. In this context, Wong et al who examined the WTP of pregnant women to have prenatal screening for the Zika virus expressed that this kind of patient has more knowledge about the risks of zika infection, and a good perception about the benefits of a zika vaccination if available, potentially compared to our interviewees [46].

According to Harapan et al, factors such as the socioeconomic level, knowledge, attitude and practice regarding dengue fever, and having personally experienced dengue fever, are associated with a greater willingness to pay for a dengue vaccine [25]. However in our study, respondents who had zika infection did not demonstrate a higher value of the willingness to pay compared with those who never had this flavivirus. This though may reflect the typical self-limiting nature of the disease.

We are aware that there are several publications involving WTP associated with vaccines. Ughasoro et al conducted a community-based cross-sectional qualitative and a quantitative interventional study among two communities in different states in Nigeria and demonstrated that more than 87.5% of respondents (582) were willing to pay for an Ebola vaccine, a high level of acceptability for a hypothetical vaccine [24]. This is perhaps not surprising given the high morbidity and mortality associated with Ebola [24]. More than 6000 individuals participated in a study in Guinea, with most agreeing that vaccines were needed to fight Ebola, reflected again by high acceptability for a hypothetical Ebola vaccine [27]. Interestingly though in a study conducted in Sierra Leone evaluating knowledge, attitudes and acceptability for an Ebola vaccine, 72.5% of the respondents were willing to be vaccinated if the vaccine was free of charge, but only 26.6% would be vaccinated if it was necessary to pay [28]. Finally, Painter et al examined the factors associated with WTP for an Ebola vaccine using the GfK Group's Knowledge Panel® and demonstrated that among participants (1,447), 40.3% would not pay for an Ebola vaccine. In addition, among the respondents who would be WTP, 66.0% would pay \$1–50; 20.1% would pay \$51–100 and only 13.9% would pay more than US\$100 [29].

Cameron and collaborators also conducted a marginal willingness-to-pay for attributes of a hypothetical HIV vaccine in Thailand [26]. The authors verified that on average respondents are more than twice as likely to accept a vaccine with a 99% efficacy compared with a vaccine with only 50% efficacy. This represented a willingness to pay of US\$383 more for a high efficacy vaccine compared with a low efficacy vaccine. These results reinforce that if a zika vaccine was approved in Brazil with a lower or higher efficacy than 80% which was utilized in our study, this would appreciably alter the willingness to pay. Nunn et al investigated the acceptability and the willingness to take and pay for an HIV self-test in a predominately African American neighborhood in the United States. Approximately 90% of respondents were willing to use an HIV self-test and 55% were willing to buy an HIV self-test; however, individuals in the low-risk class were less willing to self-test compared to those with concurrent sexual partners [30]. In another study conducted by Whittington et al to determine the demand for a hypothetical HIV vaccine in Mexico (Guadalajara), the median WTP value was US\$316 [31], which was similar to Cameron et al [26]. Individuals with higher incomes, spouses or partners, and higher perceived risks of becoming infected, were willing to pay more for the vaccine. However, older respondents would pay less [31], which is different to our study where age did not affect WTP for a hypothetical zika vaccine.

In a recent study in Vietnam conducted among 330 in-and-out patients with dengue fever, 77.3% were WTP an average of US\$ 67.4 for the vaccine [33]. More elderly patients, those with health insurance, traveling in the past 15 days, or suffering from mental health, were less likely to pay for the dengue vaccine. However, those with a longer duration of dengue, or having mobility problems, were positively associated with WTP for the dengue vaccine [33]. This is comparable to the study by Harapan et al where those who personally experienced dengue fever had a higher WTP for a dengue vaccine [25]. The average of US\$ 67.4 is though appreciably higher than the US\$33.61 (120.00BRL) for the vaccine seen in our study conducted among individuals in Brazil [22]. Finally, in a recent study conducted in rural Guatemala regarding a hypothetical vaccine for zika, whilst demand for such vaccines would be high at 50% and 75% efficacy, WTP  $\geq$ \$6.81 for the vaccine was only seen in 16 – 17% on participants [32] as zika infections are typically seen as asymptomatic or mild and congenital abnormalities are rare [32]. This is appreciably lower though than the median of US\$31.34 (BRL100.00) seen in our study. In addition, in the year that we conducted this study there was no zika outbreak in Brazil and the number of cases were reduced, which may well have influenced the maximum values of WTP among the Brazilian people in our study [26,47].

All these WTP studies reinforce the fact that there can be very different perceptions about WTP for the same vaccine in different localities and countries. In general, the residents of endemic

regions have a greater acceptability and WTP for a hypothetical vaccine than others. Knowledge is also a strong aspect influencing people's behavior towards an infection and their WTP for a therapeutic intervention [33,34]. Consequently, it is essential to undertake WTP studies in the country if such studies are to be used for pricing and funding decisions.

As mentioned, CMED establishes medicine prices for the Brazilian private system by typically referencing prices in other countries including Canada, the United States and the United Kingdom [20]. However, as also mentioned, since tropical diseases such as zika do not usually occur in these countries, it is important to conduct studies such as WTP that can assist the Brazilian government in their discussions about price setting especially for the private market. We have previously performed a similar study regarding the WTP for the Dengvaxia® at US\$33.61 (120.00/11.20BRL dose) for the three-doses (complete schedule) [22]. Our findings were presented to the CMED group in a meeting when deciding about Dengvaxia® pricing in 2016. After some analysis, CMED concluded that the Dengvaxia price may vary from US\$37.19 to US\$38.80 according to the State's (provinces) tax rates of each of the 26 States of the Brazil [48]. In view of this, WTP studies can be relevant for other infections such as zika and chikungunya as contributions to pricing discussions directly for the private market, and indirectly for the public health system, once the National Commission on Technology Incorporation of the National Health System (CONITEC) considers the CMED price setting in any analysis applied to SUS price setting [49].

Brazil has a national immunization program with coverage for an appreciable number of infectious diseases and represents almost the totality of the vaccine services in the country (approximately 95%) [50]. This program is one of SUS strategies to reduce the morbidity and mortality associated with certain infectious diseases. From prices established by CMED, which focuses on the private market, pharmaceutical companies can apply for incorporation of their new medicines, including any new vaccines, into the national health system by sending a process submission to CONITEC. As part of the decision process, CONITEC considers several distinct studies including systematic reviews of efficacy/effectiveness and safety studies, cost effectiveness analyses and other published economic studies involving the new technology [49]. Currently no zika vaccine has yet been approved in Brazil or any endemic country. According to CMED and CONITEC rules, economic studies [20,49] such as WTP [20,22, 49] can also contribute to future pricing discussions especially if such studies involve Brazilian peoples' perception about the value of a new technology such as a new zika vaccine that could be approved in the future. We believe our study represents the first economic analysis applying this methodology in Brazil. Having said this, the price finally paid by the public administration to acquire pharmaceutical products is always lower than that the price paid in the private market due to mandatory discounts known as Coefficient of Adequacy of prices. Consequently, any price negotiated by SUS for any Zika vaccine will be lower than that currently being considered by companies for the private market if they wish SUS users to have access to this new vaccine as part of any National Immunization Program [51].

We are aware though that a low willingness to pay can discourage the development and research of vaccines by pharmaceutical companies. To address this, governmental mechanisms should be established to stimulate research in this area. For this purpose, the Brazilian Funder for Innovation and Research (FINEP) has allocated US\$ 62.6 million in the form of credit to be granted to private companies for research and technological development applied to combat the virus [52]. The Ministry of Health has also allocated US\$ 1.4 million (4,400,000BRL) to FIOCRUZ for the development of a vaccine against the infection [53] especially as Zika is a neglected disease that mainly affects underdeveloped or developing countries [5].

Limitations of this study include the fact that this is a hypothetical vaccine and these values may not reflect reality at the time any new product becomes available, similar to other situations [24,26,33]. In addition, in our study, the frequency of individuals with family incomes more than 5 times the minimum wage was 68.3%, which is low compared with the average rate of 87.9% for Brazil [42]. Attaining this figure might have resulted in a higher median value of WTP for this hypothetical vaccine. Similar findings were seen in previous study conducted for CYD-TDV dengue vaccine [22]. In addition, according to the National Regulatory Agency for Private Health

Insurance and Plans (ANS), 22.9 % of the Brazilian population has health insurance, a lower value compared with 56.8% reported by the respondents in our study [54].

Despite these limitations, we believe this study should contribute to discussions around the construction of a possible vaccination program against Zika when one of the vaccines in development is available together with appropriate prices for SUS.

## 5. CONCLUSION

50% of the interviewees in Belo Horizonte and its metropolitan area were willing to pay US\$ 31.34 (100.00BRL) for this hypothetical vaccine against Zika. We believe this study can contribute to the pricing of any new vaccine in CMED, and the socioeconomic data should be useful in the discussions about the introduction of any new vaccine for Zika into the Public Health System (SUS) in Brazil. In the current economic situation in Brazil, knowing the WTP for health products and services becomes increasingly important so that any new technology can be accessible to the population in need.

### Expert Commentary

We envisage that during the coming years, new vaccines for Zika will be developed to combat the disease. We also believe that WTP studies such as these, combined with submissions by pharmaceutical companies, will help guide pricing and reimbursement decisions in Brazil for medicines to be incorporated in SUS. We will be researching and monitoring this in the future, with the aim of trying to reduce the number of cases of Zika among the population in Brazil within current resource constraints and their subsequent impact on health.

### Key issues:

- In the most recent outbreak in Brazil, 326,050 cases have been reported since 2015.
- The common symptoms associated with this infection are headache, conjunctivitis, fever, erythema, myalgia, arthralgia retro-orbital pain, anorexia, vomiting, diarrhea, and abdominal pain.
- Severe cases can be associated with neurological disorders and neonatal malformations (microcephaly).
- Until now, there has not been a specific licensed treatment for Zika, and the development of an effective vaccine against the Zika virus represents an important strategy for the control of the disease.
- This study estimated the willingness to pay (WTP) of Brazilian consumers for a hypothetical Zika vaccine through an analysis of contingent valuation.
- 50 % of the interviewees were willing to pay US\$ 31.34 (100.00BRL) for the hypothetical vaccine against Zika.
- The study can contribute to the pricing set of the vaccine, and the socioeconomic data might be useful in the discussions about the introduction of the vaccine onto the Public Health System (SUS) in Brazil and onto the market.

### AUTHOR CONTRIBUTIONS

RMJ, IG, ER, and CR undertook the study and the analysis. RMJ, IG, ER, MG, AGR, BG and CR subsequently revised the draft and produced the final and revised manuscripts. All authors approved the final and revised manuscripts. All authors also agree to be accountable for all aspects of the work.

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### Data availability

The authors can be contacted directly for further details regarding their findings.

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(\* = of importance, \*\* = of considerable importance)

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