Willingness-To-Pay for COVID-19 Vaccine in Low and Middle-Income Countries Compared to High-Income Countries: A Systematic Review

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Authors’ contributions
This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: By focusing largely on lower-income countries, this study adds to the evolving worldwide picture of willingness to pay for COVID19 vaccination. Willingness-To-Pay (WTP) values for the pandemic COVID-19 vaccine, which provide monetary indicators of community preferences for vaccines, could help policymakers in low- and middle-income countries determine priorities for health resource utilization.

Study Design: Systematic Review.

Methodology: A systematic review of the study on willingness to pay for COVID-19 vaccine in the Pubmed, Science Direct, and Scopus through January 2022 was performed to find relevant articles published between January 2020 and January 2022. Following PRISMA guidelines, the study yielded 19 English-language studies (12 studies in low- and middle-income countries, 2 in high-income countries, and 5 in upper-middle-income countries) that evaluated WTP for COVID-19 vaccines, either existing or hypothetical vaccines. All WTP values extracted were converted to 2021 United States Dollars (USD) for comparability.

Results: This study showed that the willingness to pay in low-middle-income countries varied from USD 1.2 to USD 85.92. Studies conducted in the same country might have different WTP values.

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Average WTP in low-income countries have lower WTPs than high and upper-middle-income countries. In addition to being in line with differences in GDP, cases and deaths from COVID-19 in high-income countries are higher than in low-income countries. **Conclusion:** From low-middle income countries evaluation, the high value of WTP is not consistently aligned with the high value of GDP per capita from each country. The finding demonstrates that the factors that affect the value of WTP are not only the GDP per capita of the country. The perception of risk, the WTP evaluation method used, and several other factors that need to be studied further also affect the amount of WTP.

**Keywords:** Willingness to pay; Covid-19; vaccine; low-middle-income countries.

### 1. INTRODUCTION

On January 6, 2022, 296 million confirmed cases of COVID-19 were reported to WHO, with 5.4 million deaths. United States, Europe, South East Asia, Eastern Mediterranean, Western Pacific, and Africa have the most cases [1]. In conjunction with other preventative measures, vaccination is a critical instrument in the pandemic's fight [2]. Vaccine research and development activities have commenced worldwide since the COVID-19 outbreak. A total of 9 million vaccination doses were delivered on January 4, 2022, and there were 331 vaccine candidates in clinical and preclinical research, with 137 in clinical trials [3]. According to studies, protection against COVID-19 declines over time and may potentially be reduced due to changes in circulating variations. The recent appearance of the Omicron variant emphasizes the necessity of immunization and boosters for COVID-19 protection [4]. WHO sets a strategy to Achieve Global COVID-19 Vaccination by Mid-2022, which aims to vaccinate 70% of the population in each country by the middle of this year [5]. At the time of writing, 9.4 billion doses have been delivered globally, with 29.8 million doses being administered every day [6].

At least one dose of the COVID-19 vaccine has been given to 59.1% of the world's population, but in low-income countries, just 8.9% of people have got at least one dose [6]. Achieving the vaccination target requires the role of various parties. According to the current global vaccine allocation system, a country's income levels influence vaccine access, which influences vaccine deployment and, eventually, vaccination coverage [7]. Although the effective and equitable distribution of COVID-19 vaccinations is a top governmental priority, acceptance is equally critical. Vaccination acceptance contributes to significantly higher vaccination rates among populations since the final determinant of a vaccination program's success or failure is the public [8]. Based on a previous study, vaccine uptake in the low middle-income country is generally explained by a desire for personal protection against COVID-19, with side effects being the most common cause for hesitancy. Vaccination programs should concentrate on converting high levels of claimed acceptability into actual vaccination uptake [9].

WTP is a monetary indicator of a customer's willingness to pay for a product or service [10]. In vaccination decisions, the decision to vaccinate is based on an individual's WTP for enhanced health benefits from a vaccination [11]. The evaluation of public WTP for the COVID-19 vaccine is necessary to determine the feasibility of implementing a vaccination program once the vaccine is available, as well as to provide insight into future pricing considerations, demand forecasts, and the implementation of the national COVID-19 immunization program [11].

This study focuses mainly on lower-income countries and adds to the evolving worldwide picture of willingness to pay for COVID19 vaccination. We used the 2021 World Bank classification to define countries’ income categories [12]. While our primary focus is on WTP for vaccinations in low- and middle-income countries, we also include WTP studies for vaccines in high-income countries for comparative purposes.

### 2. MATERIAL AND METHODS

#### 2.1 Search Strategy and Selection Criteria

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria were used to conduct a systematic literature search. Pubmed, Science Direct, and Scopus were among the academic topical databases, as was the Google Scholar search engine was used to search for relevant articles published between January 2020 and December 2021.
Duplicates were deleted from the retrieved articles and entered into the Zotero reference manager program. Following the screening process, the writers read the complete text of each of the studies included to determine their suitability. Full-text papers were accessed and evaluated for eligibility after irrelevant articles were removed. Studies were considered eligible if they met the following criteria: (1) were conducted in English; (2) explored COVID-19 vaccination willingness to pay; (3) used validated measuring instruments to measure willingness to pay; (4) had a full-text publication publicly available; (5) were peer-reviewed. The study that was not published in English did not have full-text publication, unrelated topics or subjects, and data in publications that could not be extracted or used for further review were excluded from this study.

2.2 Data Extraction

For data extraction, a tabular form was created. The data reflected surveyed participants’ estimated WTP values of the COVID-19 vaccine and the method used for measuring WTP. Other relevant information regarding multiple dimensions were collected for each study, including: (1) study aim, (2) target population, (3) WTP valuation methods (survey method, respondents and sample size, and valuation format). All reported WTP values were adjusted to 2021 United States dollars (USD) using GDP deflators and purchasing power parity conversion factors. We selected the year when the research's survey was performed when the original currency year was not mentioned in the study. We used the norm of presuming the currency year was the year preceding the publishing year when neither the currency year nor the survey year was available. After summarizing all the data in the tabular form, it was feasible to find all eligible trials (those that reported some of the factors associated with future COVID-19 vaccination uptake), as well as those that did not meet the inclusion criteria.

2.3 Data Presentation

All of the extracted data is shown in a tabular format. We mainly utilized the term reported in the study itself to describe the methodological techniques used for eliciting WTP values when reporting the methodological approaches used for eliciting WTP values. As a result, summaries of vaccine willingness to pay value are offered in text format based on the geographical context, followed by the primary factors contributing to the observed results.

Fig. 1. Flow diagram for the study selection process
Table 1. Summary of the characteristic of the WTP studies in vaccines

| Description | Number of studies, Sources | Low- and middle-income countries (N=12) | High-income countries (N=7) |
|-------------|---------------------------|-----------------------------------------|-----------------------------|
| Study type  |                           |                                         |                             |
| Methodological |                         | 1                                       | 1                           |
| Applied     |                           | 11                                      | 6                           |
| Valuation Method |                     | • Contingent valuation (CV)             | 4                           |
|              |                           | • Other methods                         | 8                           |
|              |                           | • No report of detailed methods          | NA                          |
| Respondent type |                     | General population                      | 11                          |
|              |                           | Healthcare providers                    | NA                          |
|              |                           | Specific population (pregnant woman)    | 1 (pregnant woman)          |

Abbreviations: NA: Not available

2.4 Critical Appraisal of Studies: Quality Assurance Process

Four-step of quality assurance were maintained: (1) Using the Zotero software, all duplicates were removed (2) The titles and abstracts of the papers discovered were examined, and those unrelated to the review were eliminated. (3) The full texts of the retained publications were examined by two authors, and any differences were resolved through discussion.

3. RESULTS AND DISCUSSION

3.1 Results

A total of 135 studies were found after doing the systematic search, with 31 articles found using PubMed, 71 articles found using Scopus, and 14 articles found using Google scholar. Based on titles and abstracts, 87 articles were removed due to their irrelevancy to the research question. After a full-text assessment of the remaining 48 papers, 29 studies that did not give WTP values for specific vaccines were eliminated, leaving 19 studies for data extraction. The articles included in this study were published after January 2020 and consist of 12 articles conducted in low and middle-income countries and seven from high and upper-middle-income countries. The summary of the characteristic shown in Table 1.

3.1.1 WTP measure for vaccines in low and middle income countries

More detailed information about 12 studies in low and middle-income countries was presented in Table 2. The study showed that WTP values and WTP scenarios varied. Most of the studies reported both mean and median values of WTP, but some of the studies only reported the mean or median value of WTP. For studies that reported both mean and median, the median value was often lower than the means value. It means that the data distribution is skewed to the right ("positively skewed" distribution).

The sample size of studies (n = 19) ranged from 440 to 3,541 participants. All of the studies were conducted online due to the pandemic condition. The method for WTP estimation method was used: contingent valuation double-bounded dichotomous (3 studies), contingent valuation single-bounded dichotomous (1 study), close-ended (6 studies), open-ended (1 study) method, including three studies that used more than one method.

The estimated value of WTP obtained from several countries varied. Among studies conducted for the same countries, the magnitude of the WTP values was also varied. For example, the study in Pakistan [13] showed the median of WTP was USD 7, while the study in Pakistan [14] showed the median of WTP was USD 3.13. Meanwhile, the WTP result in Nigeria [15] and Nigeria [16] were both USD 1.2 but in Nigeria [17] was USD 13.

In low- and middle-income countries, Fig. 2 demonstrates the relative magnitude of WTP values for several countries compared to GDP per capita in each country. The average willingness to pay in the complete set of low-middle income countries is USD 19.03, with a median of 7.04.
3.1.2 Comparison with the WTP values in high-income countries

The detailed characteristic and WTP measures for seven studies in high and upper-middle-income countries were presented in Table 3 using the same format as Table 2. WTP values in high- and upper-middle-income countries were, on average, higher than those in low- and middle-income countries. The average WTP value in the high-income country was USD 123, while in the middle-income country were USD 147.

3.1 Discussion

This review explored the willingness to pay for the COVID-19 vaccine in low-middle-income countries. The reviews used data from a total of 22,212 respondents in 19 studies from 12 low-middle-income countries such as Kenya, Indonesia, Pakistan, Vietnam, Nigeria, Ghana, Bangladesh, and India, two high-income countries such as Chile and United States, and three upper-middle-income countries such as Brazil, China, Malaysia, and Ecuador.

WTP is based on welfare economics and is frequently used to describe health benefits in monetary units in cost-benefit analysis, an economic evaluation [18]. This study showed that willingness to pay for vaccines varied among different countries. The willingness to pay for COVID-19 is correlated with the willingness to accept the COVID-19 vaccination. The higher level of effectiveness and concerns over vaccine safety was the common factor of vaccine acceptance based on the previous study [19]. Besides, monthly household income, education level, and self-diagnosis of COVID-19 or a friend, family member, or coworker are all essential factors in COVID-19 vaccination uptake [14]. All these factors may affect the decision to pay for a vaccine.

From low-middle income countries’ evaluation, the high value of WTP is not consistently aligned with the high value of GDP per capita. For example, even though Indonesia had the highest GDP per capita value in 2020 (USD 3,869.59) among the low-middle income countries in this study, the resulting WTP is not the highest. On the other hand, although Pakistan has the lowest GDP per capita in this study (USD 1,193.73), the WTP value generated is not the lowest. However, average WTP in low-income countries has lower WTPs than high and upper-middle-income countries.

![Fig. 2. The relative magnitude of WTP values for several countries compared to GDP per capita in each country](image)
Fig. 3. The relative magnitude of WTP values for low-middle-income countries compared to time of study in each country

Differences in willingness to pay can also be influenced by differences in the time of data collection. There are three groups divided based on the data collection time: March to May 2020, September to October 2020, and January to February 2021. The data taken in the first group shows a relatively high number of WTP, although the case confirmation rate was relatively low compared to the other two groups. This could be because the severity of the disease was still not widely known at that time, so the desire to get vaccines as a preventive measure is higher. The respondents deemed an unknown sickness more harmful than a condition caused by known infectious diseases [20]. Meanwhile, in the other two time groups, WTP tends to be lower. This can be due to the fact that free vaccination has been confirmed in various countries, thereby reducing the desire to pay out of pocket for the vaccine.

Studies conducted in the same country might have different WTP values. For example, in Vietnam, the study from Vo, et. al; showed USD 85.92 as WTP mean value while the study from the same country (Nguyen, et al) has a lower WTP value which is USD 15.2 [21,22]. This might happened due to the difference in respondent characteristics. The study by Nguyen et al was conducted on pregnant women. The most common reason for refusing vaccination based on the study was worry about the safety of the vaccine. Otherwise, studies that were performed in Nigeria (3 studies) have the range of USD 1.2 – 13.16 [15-17].

In-country level, several factors such as high reported COVID-19 cases and deaths might cause the higher acceptance of vaccines and affect the higher WTP value. If people believe the risk of disease is severe, they may be willing to tolerate any vaccination risks [23]. For example, Vietnam and Indonesia have the highest mean of WTP value which was USD 85.92 and 57.2 also have a higher death cumulative value in early Jan 2022, which were 34.000 and 144.000 compared to other countries in this study [24]. Otherwise, the lowest WTP value was observed in some African countries, Nigeria and Ghana. This might be caused by COVID-19 mortality is currently lower in the African countries compared to other WHO regions [1]. The perception that Africa is less in danger of COVID-19 has also prompted concerns about the need for large-scale vaccine initiatives in Africa [25].
Table 2. Willingness to Pay (WTP) valuation method and WTP values for vaccine in low-middle income countries (USD 2021)

| Study                  | Country      | Study aim                                                                                                                                                                                                 | Time of study                  | Target Population for vaccination | Methods for measuring WTP                  | Respondent (N= sample size) | Estimated mean or median WTP                        |
|------------------------|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|-----------------------------------|-------------------------------------------|-----------------------------|----------------------------------------------------|
| Capio et. al [27]     | Kenya        | 1) Measure individuals’ willingness to pay (WTP) for a COVID-19 vaccine in Kenya; 2) evaluate the effect of vaccine characteristics (duration of protection and efficacy) and individuals’ socioeconomic variables on WTP, and 3) estimate the aggregate demand and economic value of a COVID-19 vaccine. | April 7th to April 15th, 2020 | Adult CV (Double-Bounded Dichotomous) | 1,050                                      | Individuals’ mean WTP for the vaccine range from USD 49.81 to USD 68.25 (depending on vaccine characteristics) |
| Harapan et. al [28]   | Indonesia    | To measure the willingness-to-pay (WTP) for a COVID-19 vaccine and its determinants in Indonesia                                                                                                           | March 25th to April 6th, 2020 | Adult CV (Single-Bounded Dichotomous) | 1,359                                      | The mean WTP of USD 57.20 and median WTP of USD 30.94 |
| Tahir, et. al [14]    | Pakistan     | To assess the Pakistani population’s attitude and preferences towards the Coronavirus disease 2019 (COVID-19) vaccine                                                                                 | September 27th to October 11th, 2020 | Adult Close ended question | 883                                        | 33.9% (n=212) were willing to pay up to 7 USD (1000 PKR) for the COVID-19 vaccine |
| Arshad, et. al [13]   | Pakistan     | To evaluate the acceptance rate, willingness to pay, and preference for COVID-19 vaccines in the general public of Pakistan                                                                              | the month of January 2021     | Adult Close ended question     | 2,158                                      | Median of willingness to pay less than 3.12 USD (500 PKR) (52.7%) |
| Vo, et. al[23]        | Vietnam      | To evaluate willingness to pay (WTP) for a future COVID-19 vaccination among young adults in Southern Vietnam                                                                                           | 2 weeks in May 2020           | Adult CV (double-bounded dichotomous choice) | 495                                        | The mean of willing to pay for the vaccine was USD 85.92±69.01 |
| Adigwe, et. al[15]    | Nigeria      | To investigate factors associated with vaccine hesitancy and willingness to pay for COVID-19 vaccination                                                                                                 | the month of January 2021     | Adult Close ended question     | 1,767                                      | The median of willing to pay were 1.21 USD (500 naira) or less |
| Ilensanmi, et. al[17] | Nigeria      | To assess the perception of community members and willingness to pay for the prospective COVID-19 vaccine in Ibadan, Nigeria                                                                           | September 2020 15 years and above | Adult Close ended question | 440                                        | The median of willing to pay were USD 13.16 (5000 naira) or above |
| Okafor, et. al[16]    | Nigeria      | To evaluate the acceptability and willingness to pay for a hypothetical vaccine that is effective against COVID-19 among Nigerian citizens                                                              | October 18th and October 30th, 2020 | Adult Open ended question | 689                                        | The median range of WTP was between USD 1.2 - 2.5 (500-1000N) |
| Study                | Country      | Study aim                                                                 | Time of study                          | Target Population for vaccination | Methods for measuring WTP               | Respondent (N= sample size) | Estimated mean or median WTP |
|---------------------|--------------|----------------------------------------------------------------------------|----------------------------------------|------------------------------------|----------------------------------------|-----------------------------|-------------------------------|
| Alhassan, et. al[24]| Ghana        | To ascertain the predictors of citizens’ probability of participating in a COVID-19 vaccine trial and subsequently accept the vaccine when given the opportunity | September 18th to 23rd October, 2020    | Adult                              | Closes ended and open ended question   | 1,556                       | The mean of WTP was US$7.0 (38.82 cedi) for full vaccination |
| Kabir, et. al[29]   | Bangla-desh  | To reports the intent to receive a SARS-COV-2 vaccine, its predictors and willingness to pay in Bangladesh. | January 20th to 27th 2021               | Adult                              | Closes ended and open ended question   | 697                         | The median amount that they are willing to pay is USD 7.08 |
| Nguyen, et. al[30]  | Vietnam      | To assess acceptance of COVID-19 vaccination and the willingness to pay (WTP) for it, and investigate associated factors among pregnant women in Vietnam. | January to February 2021               | Pregnant woman                     | Open ended question                   | 651                         | The mean amount of WTP of USD 15.2 (SD ± 27.4) (from 82.6% of the total pregnant women) |
| Goruntla et. al[31] | India        | To determine the predictors of acceptance and willingness to pay (WTP) for the COVID-19 vaccine among the Indian public and to provide insights for future demand forecasts and pricing considerations. | October 5th to 20th 2020               | Adult                              | Close ended question                  | 2,451                       | The majority (2 162, 88.21%) of respondents were willing to pay an amount of INR: 500-1 000 or USD: 6.81-13.62 for a dose of COVID-19 vaccine, with a median of INR: 500 or USD 6.81 |
Table 3. Willingness to Pay (WTP) valuation method and WTP values for vaccine in high and middle income countries (USD 2021)

| Study                  | Country      | Study aim                                                                                                                                                                                                 | Time of study                  | Target Population for vaccination | Methods for measuring WTP                  | Respondent (N=sample size) | Estimated mean or median WTP |
|-----------------------|--------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|-----------------------------------|--------------------------------------------|----------------------------|----------------------------|
| Cerda, et. al[32]     | Chile        | To estimate the willingness-to-pay (WTP) value for a vaccine for COVID-19                                                                                                                                   | July 10th to August 10th 2020 | Adult                             | CV (Double-Bounded Dichotomous)            | 531                        | The mean of WTP for individual was USD 184.72 |
| Cerda, et. al[33]     | Chile        | To estimate the willingness-to-pay (WTP) value for a vaccine for COVID-19. We also identify the variables that influence individual vaccination decisions, which could be used in the design of vaccination promotion strategies. | July 10th to August 10th 2020 | Adult                             | CV (Double-Bounded Dichotomous)            | 531                        | The mean of WTP for individual was USD 232 |
| Catma, et. al[34]     | United States| To estimate the individual willingness to pay (WTP) for a COVID-19 vaccine and evaluate its predictors in the United States.                                                                           | The first week of November 2020 | Adult                             | CV (Single-Bounded Dichotomous)            | 1,285                      | The mean WTP for a vaccine with a 95 percent efficacy rate and 3-year protection (USD 318.76) was approximately 35% greater than the vaccine with a 50 percent efficacy rate and 1-year protection (USD 236.85) |
| Sarasty, et. al[35]   | Ecuador      | To evaluate the demand for a COVID-19 vaccine in Ecuador by estimating individuals’ willingness to pay (WTP) for the vaccine, and by assessing the effect of vaccine attributes (duration of protection and efficacy) and individuals’ characteristics on this valuation                                              | April 2nd to 7th, 2020        | Adult                             | CV (Double-Bounded Dichotomous)            | 1,050                      | The mean WTP values ranged from USD 147.61 to 196.65 and the median WTP from USD 76.9 to 102.5 |
| Wang, et. al[36]      | China        | To investigate individuals’ WTP and financing mechanism preference for COVID-19 vaccination during the pandemic period in China                                                                            | March 1st to 18th, 2020      | Adult                             | CV (open-ended (OE) format and payment scale (PS) format) | 2,058                      | The individuals’ mean WTP for full COVID-19 vaccination was CNY 254 (USD 36.8) with median |
| Study                  | Country | Study aim                                                                 | Time of study          | Target Population for vaccination | Methods for measuring WTP                                                                 | Respondent (N= sample size) | Estimated mean or median WTP |
|-----------------------|---------|---------------------------------------------------------------------------|------------------------|-----------------------------------|-------------------------------------------------------------------------------------------|-----------------------------|-----------------------------|
| Dias-Godói et. al[37] | Brazil  | to estimate the Brazilian consumers' WTP for a hypothetical vaccine to COVID-19 prevention to contribute to the debate and pharmacoeconomics reviews focusing on demand and potential prices for this type of medicine in Brazil starting with the private market | Not mentioned          | Adult                            | Discrete Choice, Bidding Game, and Open-Ended                                             | 1,402                       | The median of the 'maximum amount that would pay for the vaccine is USD 22.18 (120.00 BRL) of CNY 100 (USD 14.5) |
| Wong, et. al[38]      | Malaysia| To provide insights into future demand forecasts and pricing considerations | April 3rd to 12th 2020 | Adult                            | Close ended question                                                                  | 1,159                       | The mean of willing to pay for a dose of COVID-19 vaccine was USD 30.66 (MYR 134.0). The median of willing to pay was USD 23 (MYR 100)(28.9%) and USD 11.5 (MYR 50) (27.2%) |
When compared to high and upper-middle-income countries, the value of WTP is lower than low and middle-income countries. In addition to being in line with differences in GDP, cases and deaths from COVID-19 in high-income countries are higher than in low-income countries. As of early January 2022, WHO reported 152 million cases and 5.2 million deaths in high-income countries, 96 million cases and 2.3 million deaths in upper-middle-income countries, 56 million cases, and 900 thousand deaths in lower-middle-income countries, and 1.7 million cases and 40 thousand deaths in low-income countries [1].

Most of the included studies used closed-ended methods for the estimation of WTP. The closed-ended WTP structure provides much higher valuations in the health care environment than the open-ended or payment scale formats. Besides, if all other factors are equal, using a close-ended instrument instead of an open-ended or payment scale format will result in significantly higher WTP values [26].

In some studies, methods reporting is frequently incomplete. The sampling technique, response rate, and valuation period were frequently not stated. The currency year for the WTP values was not provided for all research in some studies. More comprehensive and standardized reporting would increase comparability between vaccinations and studies, making the estimates more helpful to decision-makers.

However, several limitations of our study need to be mentioned. Due to the online approach of the survey, there was an uneven distribution of participants from different countries. Besides, due to the small number of studies identified and insufficient comparability among studies, the number of countries taken as representatives of each type of income is limited. In addition, the use of online methods also limits the survey to only populations who understand literacy so that the results are less representative of the non-literate population.

Despite these limitations, our review provides a systematic and thorough overview of research evaluating WTP, a key indicator of COVID-19 vaccination economic value in low- and middle-income countries. Such assessments provide valuable information to policymakers attempting to improve the health of their communities while working with limited resources.

4. CONCLUSION

According to the findings of this study, the high value of WTP is not consistently aligned with the high value of GDP per capita from each country. The finding demonstrates that the factors that affect the value of WTP are not only the GDP per capita of the country. The perception of risk, the WTP evaluation method used, and several other factors that need to be studied further also affect the amount of WTP.

DISCLAIMER

The products used for this research are commonly and predominantly used products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by the personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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