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# A cross-sectional survey to evaluate prescribers' knowledge and understanding of safety messages following Dengvaxia® product information update

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## Abstract

**Purpose:** We evaluated the effectiveness of additional risk minimisation measures (aRMMs; i.e., educational materials) distributed to prescribers to ensure that only individuals with evidence of prior dengue infection (PDI, i.e., dengue seropositive) would be vaccinated with the tetravalent dengue vaccine (CYD-TDV; Dengvaxia®).

**Methods:** A survey was conducted in 2020 among 300 CYD-TDV prescribers in Brazil and Thailand to ascertain three success criteria: prescribers' awareness of the materials (receiving and reading them); knowledge of the key messages; and whether their self-reported behaviour regarding practice-related scenarios was aligned with the updated guidance.

**Results:** The aRMMs were not generally effective as <80% of prescribers in both countries met two of the three predefined success criteria. In Brazil, 98.7% were aware of the aRMMs whereas in Thailand this criterion was fulfilled by 74.0%. Almost all prescribers knew that CYD-TDV was recommended only in individuals with PDI (98.7% and 96.7% in Brazil and Thailand, respectively). In Brazil, where vaccination was restricted to those with a documented history of PDI, 11.3% considered that confirmation should be done through a blood test. More than 75% in both countries considered additional signs of dengue, as early warning signs, and not only those regarded as such by the 2009 WHO guidelines.

**Conclusions:** These results do not support that the aRMMs were effective as the predefined success criteria were not met. The use of reliable rapid diagnosis tests together with the revised prescribing information and educational materials will facilitate the implementation and compliance with pre-vaccination screening for CYD-TDV eligibility.

KEYWORDS

dengue, Dengvaxia, post-authorisation safety study, prescribing behaviour, risk minimisation measures, vaccine

**Key points**

- The majority of CYD-TDV prescribers (98.7% and 74.0% in Brazil and Thailand, respectively) were aware of the aRMMs.
- Almost all knew that CYD-TDV was recommended in patients with prior dengue infection only (98.7% and 96.7% in Brazil and Thailand, respectively).
- The fact that there were no reliable RDTs at time of the survey may explain why only 11.3% of prescribers in Brazil, where a pre-screening vaccination strategy is endorsed, considered that a confirmatory laboratory test was needed in all cases.
- Prescribers considered additional signs and symptoms as dengue early warning signs than those introduced by the WHO in 2009.

## 1 | INTRODUCTION

The live, attenuated, tetravalent dengue vaccine (CYD-TDV; Dengvaxia®, Sanofi Pasteur) was first approved for the prevention of dengue disease caused by the four dengue virus serotypes in individuals (aged 9 or 12 years through to 16, 45, or 60 years, depending on country approval) living in endemic areas in December 2015. This approval was based mainly on findings from one phase IIb and two phase III safety and efficacy studies involving >35 000 children living in endemic countries in Asia and Latin America.[1–3] Initial long-term safety follow-up suggested, however, that those vaccinated with CYD-TDV without a history of prior dengue infection (PDI) (i.e. dengue seronegative at baseline) were at increased risk of hospitalisation or clinically severe dengue on subsequent breakthrough 'wild-type' dengue infection.[4] This increased risk was subsequently confirmed,[5] which led the World Health Organisation (WHO) to recommended that only individuals with evidence of PDI should be vaccinated, and that countries considering routine dengue vaccination should use a pre-vaccination screening strategy to avoid vaccinating those dengue seronegative (i.e., dengue naïve).[6] Vaccination could be considered without screening in areas with ≥80% dengue seroprevalence by age 9 years (population seroprevalence criteria).[6]

To avoid the risk of severe and/or hospitalised dengue following vaccination in individuals not previously infected with the dengue virus, the CYD-TDV prescribing information was updated to limit the use of the vaccine to individuals previously exposed to dengue virus and included warnings and precautions for seronegative individuals. To inform healthcare professionals (HCPs) of the updated indication so as to avoid vaccination of seronegative individuals, Sanofi Pasteur updated the international Risk Management Plan* for CYD-TDV including additional risk minimisation measures (aRMMs) that were endorsed by the health authority.† The main aRMM was an educational guide targeting HCPs, developed by Sanofi Pasteur to reinforce the prescriber's awareness of the risk to individuals not previously infected with the dengue virus, to provide guidance on how to assess the likelihood of PDI in such individuals before vaccinating, and to increase awareness of the dengue early warning signs (from the WHO 2009 dengue case definition).[7] In Brazil, the guide was distributed by Sanofi Pasteur by email in Q1 2019 to the medical specialities likely to prescribe CYD-TDV. In Thailand, health authorities preferred to use an alternative means for risk communication: the Paediatric Infectious Disease Society of Thailand (PIDST) and the Infectious Disease Association of Thailand (IDAT) jointly developed a guidance document which they posted on their medical societies' websites. An initial communication was issued in September 2018 after the WHO preliminary recommendations and another in April 2019 after the Strategic Advisory Group of Experts (SAGE) on Immunisation meeting. In addition, the guidance issued by PIDST and IDAT was also distributed by Sanofi Pasteur in paper form by mail in 2019. The content of the guidance reflected the updated prescribing information in each country. In Brazil, vaccination was restricted to individuals with documented history of PDI (dengue positive laboratory result; i.e., pre-vaccination screening strategy). In Thailand, there were scenarios where documentation of PDI through a positive laboratory dengue result was not necessary, for example, in children aged >9 years living in the same household as a family member with dengue, and in adults, since dengue seroprevalence was >90% in this age group (population seroprevalence criteria).[8]

Here, we report a post-authorisation safety study undertaken in Brazil and Thailand to evaluate the effectiveness of the aRMM (i.e., the distributed educational materials) in the two countries by assessing prescribers' awareness of the materials, their knowledge of the key safety messages and to determine if their self-reported behaviour regarding practice-related scenarios were aligned with the updated guidance.

## 2 | METHODS

### 2.1 | Study design

This was a cross-sectional, survey conducted among CYD-TDV prescribers in Brazil and Thailand (NCT04170140). These two countries were selected based on commercial availability of Dengvaxia® and completion of aRMMs distribution. A questionnaire was developed with single and multi-choice responses (see Supplementary Methods S1). The same questionnaire (translated in local language as appropriate and adapted to the recommendations applicable in each country) with similar response outcomes was used in both participating countries. Only the mode of questionnaire administration differed to adapt

to the country's cultural preferences; online web questionnaire in Brazil or through face-to-face questionnaire administration in Thailand. Data collection started 6–12 months after the distribution of the aRMMs and lasted for 12 weeks (7 January to 25 February 2020 in Brazil, and 9 January to 10 March 2020 in Thailand). In Brazil, the risk of dengue is present during the year throughout the country and usually highest during the rainy season, typically from January to May.[9] In Thailand, the risk of dengue is also present during the year throughout the country and usually highest during the rainy season, typically from May to October.[10]

## 2.2 | Participants

All prescribers of CYD-TDV (current or past [i.e., those who prescribed or did not prescribe after the date of aRMMs distribution, respectively]) in the two countries were targeted for inclusion. The study targeted both current and past prescribers because the aRMMs were sent to all potential prescribers, and even though some may have stopped prescribing after the new information was received, they nevertheless remained potential prescribers. Prescribers were excluded if they had conflicts of interest with the survey (e.g., employed by regulatory bodies or worked in pharmaceutical industries) or had earlier participated in testing of the questionnaire. Target prescribers corresponded to the specialties who prescribe CYD-TDV in each country: GP/internist, paediatrician, and infectious disease specialist (in both Brazil and Thailand) and allergist/immunologist and endocrinologists (in Brazil only). Prescribers in each country were randomly selected from physician panels using random stratified sampling methodology; those identified were contacted by email, phone, face-to-face visit, or letters to participate (see Supplementary Methods S1).

## 2.3 | Assessment outcomes

Prescribers were evaluated in their: (1) awareness of aRMMs (receiving and reading the aRMMs), (2) knowledge of the key messages in the materials (updated prescribing information, how to assess likelihood of previous dengue, and knowledge of dengue early warning signs), and (3) behaviour regarding CYD-TDV prescriptions in practice (adherence to the key messages). Each of these three outcomes of interest were assessed using specific groups of questions (see Table S1). Each question included correct and incorrect statements. The questions that covered only key messages (i.e. receipt and reading of the aRMMs and knowledge and adherence to key safety messages) required all statements to be answered correctly (complete success), while other questions which also covered additional topics were considered successfully answered if the participant correctly answered the key statements regardless of whether the additional statements were also correct (partial success admitted). A prescriber was considered successful for the awareness outcome if at least 1 of the 2 awareness questions were successfully answered; successful for the knowledge outcome if at least 3 of the 4 knowledge questions were successfully answered; and successful for the behaviour outcome if the 2 behaviour questions were successfully answered.

The success criteria for each respective outcome (awareness, knowledge, and behaviour) were defined as 80% or more of the participants being successful for the outcome. This threshold was based on US-FDA recommendations on survey methodology for assessing risk evaluation and mitigation strategies.[11] Overall, the aRMMs were considered effective if at least two of the three outcomes were successful.

## 2.4 | Statistical analysis

The normal approximation to the binomial distribution was used for sample size determination. The proportion of interest was not known for each specific objective, and as such, we consider it to be 50% (maximum uncertainty), which yields the most conservative sample size (i.e., the largest sample size). A sample of 300 completed questionnaires was considered to provide a precision level of 5.66% across the target population. A pragmatic split across the two countries of 150 prescribers per country was implemented. All the analyses were descriptive. Categorical variables were described as the total number and relative percentage per category. The 95% confidence intervals (CI) were calculated using the Clopper Pearson exact method. Only completed questionnaires were analysed.

# 3 | RESULTS

Although the analysis was initially planned to be conducted 'overall' (both countries combined), the data are presented separately by country as the results observed in each country were highly heterogeneous.

## 3.1 | Brazil

Overall, 929 prescribers were invited; 644 (69.3%) agreed to participate. There were 468 failed screenings: 252 (53.9%) were employed by a pharmaceutical company or regulatory body; 126 (26.9%) had never prescribed CYD-TDV; and 90 (19.2%) declared a lack of patients administered with CYD-TDV prior to the survey. Twenty-six (4.0%) prescribers started the questionnaire but were screened-out after entering their specialty since the target for that specialty had been met. The response rate was 16.1% (150/929). The characteristics of the Brazilian prescribers are summarised in Table 1. The majority (>80%) reported prescribing CYD-TDV to >300 patients, and all continued prescribing after distribution of the aRMM in the country.

### 3.1.1 | Awareness of aRMM

The "awareness" criterion was successfully fulfilled as almost all (98.7%; 148/150) had received and read the aRMM (Figure 1) as

**TABLE 1** Characteristics of participants in Brazil

| Characteristics | Past prescribers[a] (*N* = 0) | Current prescribers[a] (*N* = 150) | Overall (*N* = 150) |
|---|---|---|---|
| Gender | | | |
| Male | - | 83 (55.3%) | 83 (55.3%) |
| Female | - | 65 (43.3%) | 65 (43.3%) |
| Not disclosed | - | 2 (1.3%) | 2 (1.3%) |
| Age group | | | |
| <30 years | - | 1 (0.7%) | 1 (0.7%) |
| 30–39 years | - | 19 (12.7%) | 19 (12.7%) |
| 40–49 years | - | 124 (82.7%) | 124 (82.7%) |
| 50–59 years | - | 5 (3.3%) | 5 (3.3%) |
| ≥60 years | - | - | - |
| Not disclosed | - | 1 (0.7%) | 1 (0.7%) |
| Years of experience in the specialisation | | | |
| <1 year | - | 2 (1.3%) | 2 (1.3%) |
| 1–5 years | - | - | - |
| 6–10 years | - | 4 (2.7%) | 4 (2.7%) |
| >10 years | - | 144 (96.0%) | 144 (96.0%) |
| Type of setting (multiple answers)[b] | | | |
| Private office | - | 93 (62.0%) | 93 (62.0%) |
| Private clinic | - | 43 (28.7%) | 43 (28.7%) |
| Private hospital | - | 11 (7.3%) | 11 (7.3%) |
| Public hospital | - | 2 (1.3%) | 2 (1.3%) |
| Community health centre | - | 1 (0.7%) | 1 (0.7%) |
| Other | - | 1 (0.7%) | 1 (0.7%) |
| Speciality | | | |
| General practice/Internal medicine | - | 50 (33.3%) | 50 (33.3%) |
| Paediatrician | - | 40 (26.7%) | 40 (26.7%) |
| Infectious disease specialist | - | 20 (13.3%) | 20 (13.3%) |
| Allergist/Immunologist | - | 20 (13.3%) | 20 (13.3%) |
| Endocrinologist | - | 20 (13.3%) | 20 (13.3%) |
| Number of patients having a prescription of CYD-TDV since its launch in Brazil per prescriber | | | |
| Mean (SD) | - | 379.6 (107.48) | 379.6 (107.48) |
| Median | - | 400.0 | 400.0 |
| Q1–Q3 | - | 304.0–460.0 | 304.0–460.0 |
| Interquartile range | - | 156.0 | 156.0 |
| Range (min, max) | - | (58.0, 500.0) | (58.0, 500.0) |
| Per level *n* (%) | - | | |
| <50 patients | - | - | - |
| 50–149 patients | - | 5 (3.3%) | 5 (3.3%) |
| 150–299 patients | - | 21 (14.0%) | 21 (14.0%) |
| 300–449 patients | - | 72 (48.0%) | 72 (48.0%) |
| ≥450 patients | - | 52 (34.7%) | 52 (34.7%) |
| Number of patients having a prescription of CYD-TDV *since March 2019* (after RMM in Brazil) | | | |
| Mean (SD) | - | 68.8 (38.44) | 68.8 (38.44) |
| Median | - | 56.5 | 56.5 |
| Q1–Q3 | - | 46.0–79.0 | 46.0–79.0 |
| Interquartile range | - | 33.0 | 33.0 |
| Range (min, max) | - | (20.0, 210.0) | (20.0, 210.0) |

(Continues)

**TABLE 1** (Continued)

| Characteristics | Past prescribers[a] (*N* = 0) | Current prescribers[a] (*N* = 150) | Overall (*N* = 150) |
|---|---|---|---|
| Per level *n* (%) | - | | |
| <50 patients | - | 48 (32.0%) | 48 (32.0%) |
| 50–99 patients | - | 79 (52.7%) | 79 (52.7%) |
| 100–149 patients | - | 12 (8.0%) | 12 (8.0%) |
| ≥150 patients | - | 11 (7.3%) | 11 (7.3%) |

*Note*: "-" means no results in this category (=0).
Abbreviations: CYD-TDV, Dengvaxia®; *N*, study population; Q1, lower quartile; Q3; upper quartile; RMM; risk minimisation measures; SD, standard deviation.
[a]Current prescribers defined as those who prescribed CYD-TDV after the date of RMMs distribution and past prescribers as those who did not prescribe CYD-TDV after the date of RMMs distribution.
[b]Multiple answers were possible and as such, the total might exceed 100%.

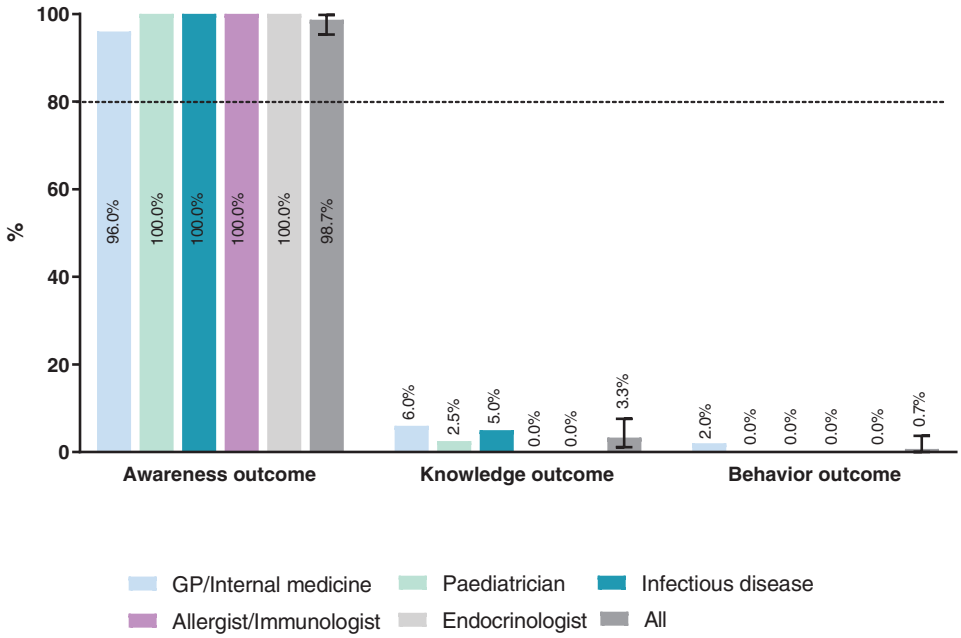


**FIGURE 1** Analysis of the three outcomes success criteria separately and per speciality in Brazil. Confidence intervals are presented as "whiskers" on the bar for "All" category. Criterion of success No 1: Awareness—Prescribers with at least 1 of 2 questions successfully answered. Criterion of success No 2: Knowledge—Prescribers with at least 3 of 4 questions successfully answered. Criterion of success No 3: Behaviour—Prescribers with the 2 questions successfully answered. Since these 3 criteria are independent, the total could exceed 100%. The threshold for considering each outcome successful was ≥80% of prescribers meeting the success conditions (dashed line).

assessed by questions (Q) 22-23. In addition, all participants had been informed about the label update (Q20) by at least one of the credible sources of information. Table S2 summarises the 'aRMM awareness' responses by prescriber speciality.

### 3.1.2 | Knowledge about aRMM

The "knowledge" criterion was not successfully fulfilled as only 3.3% (5/150) met the required conditions (Figure 1). Almost all prescribers (98.7%; 148/150) knew that CYD-TDV was recommended only in those with PDI (Q12). However, only 1.3% ($n = 2$) correctly indicated that individuals not previously infected with the dengue virus were at increased risk of severe dengue and consequent hospitalisation following vaccination with CYD-TDV (Q13). In addition, 96.0% (144/150) knew that PDI should be confirmed before administering CYD-TDV, but only 17 (11.3%) considered that confirmation should be done through a laboratory blood test (Q14). Few participants knew that CYD-TDV was not recommended in individuals travelling to endemic areas if they lived in a non-endemic area ($n = 2$ for Q12 and $n = 4$ for Q14). The true early dengue warning signs were correctly identified by 70.0–94.7% (Q15). However, 98.7% (148/150) and 74.7% (112/150) also considered 'bone pain' and 'rash', respectively, which are not early dengue warning signs. Overall, only one participant correctly identified the true and false responses for questions on early warning signs of dengue. Table S3 summarises the 'knowledge' responses by prescriber group.

### 3.1.3 | Self-reported behaviour

The "self-reported behaviour" criterion was not successfully fulfilled as only 0.7% (1/150) met the required conditions (Figure 1). All participants, except one, correctly identified the scenarios presenting a

patient eligible for vaccination (Q18). However, the majority (>96%) also considered the following incorrect scenarios as eligible: adult living in an endemic area claiming to have had dengue but with no supportive clinical records or laboratory results; adult living in an endemic area with negative laboratory results for PDI; and adult living in a non-endemic area and travelling to an endemic area with no supportive clinical records or laboratory results (Q18). The majority (>89%) would inform patients that they needed to continue taking preventive measures against mosquito bites and seek medical care if they develop signs of dengue. However, while 97.3% (146/150) would inform their patients about the true early dengue warning signs, 78.0% (117/150) also selected they would communicate about rash and bone pain, which were not early warning signs of dengue (Q19). Table S4 summarises the 'self-reported behaviour' responses by prescriber group.

## 3.2 | Thailand

In Thailand, 386 prescribers were invited; of these 281 (72.8%) agreed to participate. There were 126 failed screenings: 4 (3.2%) were employed by a pharmaceutical company or regulatory body; 1 (0.8%) had never prescribed CYD-TDV; and 121 (96.0%) declared a lack of patients administered with CYD-TDV prior to the survey. Five participants had started the questionnaire in the system but were screened-out after entering their prescriber specialty since the target for that specialty had been met. The response rate was 38.9% (150/386). The characteristics of the Thai prescribers are summarised in Table 2. The vast majority (98.7%) reported prescribing CYD-TDV to <50 patients. Approximately 25% did not prescribe after the release of the aRMM, due mainly to concerns with vaccine safety or effectiveness.

### 3.2.1 | Awareness of aRMM

The "awareness" criterion was not fulfilled as 74.0% (111/150) met the required conditions (Figure 2). Only 18.7% (28/150) reported they had been informed about the updated CYD-TDV label (Q20). However, approximately 70.0% reported that they had received (Q22) and read (Q23) the guidance for the use of CYD-TDV issued by the PIDST and the IDAT. Table S5 summarises the 'awareness' responses by prescriber group. When considering the three specialties, paediatricians and infectious disease prescribers met the awareness criteria (84.0% and 85.0%, respectively) while GP/internal medicine HCPs did not (58.3%).

### 3.2.2 | Knowledge about aRMM

The "knowledge" criterion was not successfully fulfilled as only 31.3% met the required conditions (Figure 2). Although almost all participants (96.7%; 145/150) correctly knew that CYD-TDV was recommended in individuals with PDI, only 78.0% (117/150) also knew it was not recommended in individuals with no PDI (Q12). About half correctly indicated that individuals not previously infected by dengue were at increased risk of severe dengue and consequent hospitalisation following vaccination with CYD-TDV (Q13). In addition, 83.3% (125/150) of the prescribers knew that PDI should be confirmed before administering CYD-TDV in children. However, less prescribers, 68.7% (103/150), knew that "the likelihood of PDI should be confirmed through a laboratory test, unless an adult living in an area with high seroprevalence of dengue" (Q14). Approximately two-thirds knew that CYD-TDV was not recommended in individuals travelling to endemic areas if they lived in a non-endemic area (Q12 and Q14). The early dengue warning signs were correctly identified by 37.3%–69.3% of the participants (Q15). However, a majority also incorrectly considered 'bone pain' (78.0%; 117/150) and 'rash' (54.7%; 82/150) to be early warning signs of dengue. Overall, only three participants correctly identified the true and false responses for questions on early warning signs of dengue. Table S6 summarises the 'knowledge' responses by prescriber group.

### 3.2.3 | Self-reported behaviour

The "self-reported behaviour" criterion was not successfully fulfilled as only 24.7% met the required conditions (Figure 2). All prescribers, except four, correctly identified the scenarios presenting a patient eligible for vaccination. In addition, 74.7% (112/150) also correctly identified that an adult living in an endemic area with negative laboratory test results for PDI was not eligible for vaccination, and 68.0% (102/150) also correctly identified that an adult living in a non-endemic area and travelling to an endemic area with no supportive clinical records or laboratory results was not eligible. However, 67.3% (101/150) incorrectly considered that a child living in endemic area with no supportive clinical records or laboratory results, but whose parents claimed the child has had dengue in the past, was eligible for vaccination (Q18).

More than 90% of prescribers would inform patients that they needed to continue taking preventive measures against mosquito bites and seek medical care if they develop signs of dengue. When asked if patients should seek medical care if they developed haemorrhagic fever, which is an early dengue warning sign, 92.7% (139/150) correctly answered affirmatively. However, 84.7% (127/150) also responded that patients should remain vigilant for dengue early warning signs, such as rash or bone pain, which are not early warning signs of dengue (Q19). Table S7 summarises the 'self-reported behaviour' responses by prescriber group.

## 4 | DISCUSSION

Our study suggests that the aRMMs used were not successful as per the predefined success criteria (i.e. two of the three outcomes assessed successfully met by 80% of the participants) in both countries, but this generalisation needs to be interpreted with caution. On the one hand, the predefined threshold was conservative and arbitrary

**TABLE 2** Characteristics of participants in Thailand

| Characteristics | Past prescribers[a] (*N* = 38) | Current prescribers[a] (*N* = 112) | Overall (*N* = 150) |
|---|---|---|---|
| Gender | | | |
| Male | 19 (50.0%) | 55 (49.1%) | 74 (49.3%) |
| Female | 19 (50.0%) | 57 (50.9%) | 76 (50.7%) |
| Not disclosed | - | - | - |
| Age group | | | |
| <30 years | 1 (2.6%) | 2 (1.8%) | 3 (2.0%) |
| 30–39 years | 18 (47.4%) | 39 (34.8%) | 57 (38.0%) |
| 40–49 years | 9 (23.7%) | 40 (35.7%) | 49 (32.7%) |
| 50–59 years | 5 (13.2%) | 25 (22.3%) | 30 (20.0%) |
| ≥60 years | 5 (13.2%) | 6 (5.4%) | 11 (7.3%) |
| Not disclosed | - | - | - |
| Years of experience in the specialisation | | | |
| <1 year | 1 (2.6%) | - | 1 (0.7%) |
| 1–5 years | 6 (15.8%) | 17 (15.2%) | 23 (15.3%) |
| 6–10 years | 15 (39.5%) | 31 (27.7%) | 46 (30.7%) |
| >10 years | 16 (42.1%) | 64 (57.1%) | 80 (53.3%) |
| Type of setting (multiple answers)[a] | | | |
| Private hospital | 30 (78.9%) | 91 (81.3%) | 121 (80.7%) |
| Public hospital | 22 (57.9%) | 39 (34.8%) | 61 (40.7%) |
| Private clinic | 2 (5.3%) | 5 (4.5%) | 7 (4.7%) |
| Private office | 1 (2.6%) | - | 1 (0.7%) |
| Community health centre | - | - | - |
| Other | - | - | - |
| Speciality | | | |
| General practice/Internal medicine | 17 (44.7%) | 43 (38.4%) | 60 (40.0%) |
| Paediatrician | 15 (39.5%) | 35 (31.3%) | 50 (33.3%) |
| Infectious disease specialist | 6 (15.8%) | 34 (30.4%) | 40 (26.7%) |
| Number of patients having a prescription of CYD-TDV since its launch in Thailand per prescriber | | | |
| Mean (SD) | 5.6 (4.51) | 10.4 (15.99) | 9.2 (14.14) |
| Median | 5.0 | 5.5 | 5.0 |
| Q1–Q3 | 3.0–5.0 | 3.0–10.0 | 3.0–10.0 |
| Interquartile range | 2.0 | 7.0 | 7.0 |
| Range (min, max) | (2.0, 25.0) | (1.0, 150.0) | (1.0, 150.0) |
| Per level *n* (%) | | | |
| <50 patients | 38 (100.0%) | 110 (98.2%) | 148 (98.7%) |
| 50–149 patients | - | 1 (0.9%) | 1 (0.7%) |
| 150–299 patients | - | 1 (0.9%) | 1 (0.7%) |
| 300–449 patients | - | - | - |
| ≥450 patients | - | - | - |
| Number of patients having a prescription of CYD-TDV *since September 2018* (after RMM in Thailand) | | | |
| Mean (SD) | NA | 6.3 (15.01) | 6.3 (15.01) |
| Median | NA | 3.0 | 3.0 |
| Q1–Q3 | NA | 2.0–5.0 | 2.0–5.0 |
| Interquartile range | NA | 3.0 | 3.0 |
| Range (min, max) | NA | (1.0, 150.0) | (1.0, 150.0) |

**TABLE 2** (Continued)

| Characteristics | Past prescribers[a] (*N* = 38) | Current prescribers[a] (*N* = 112) | Overall (*N* = 150) |
|---|---|---|---|
| Per level *n* (%) | | | |
| <50 patients | NA | 111 (99.1%) | 111 (99.1%) |
| 50–99 patients | NA | - | - |
| 100–149 patients | NA | - | - |
| ≥150 patients | NA | 1 (0.9%) | 1 (0.9%) |

*Note*: "-" means no results in this category (=0).
Abbreviations: CYD-TDV, Dengvaxia®; N, study population; Q1, lower quartile; Q3; upper quartile; RMM; risk minimisation measures; SD, standard deviation; NA, not applicable.
[a]Current prescribers defined as those who prescribed CYD-TDV after date of RMMs distribution and past prescribers as those who did not prescribe CYD-TDV after date of RMMs distribution.
[b]Multiple answers were possible and as such, the total might exceed 100%.

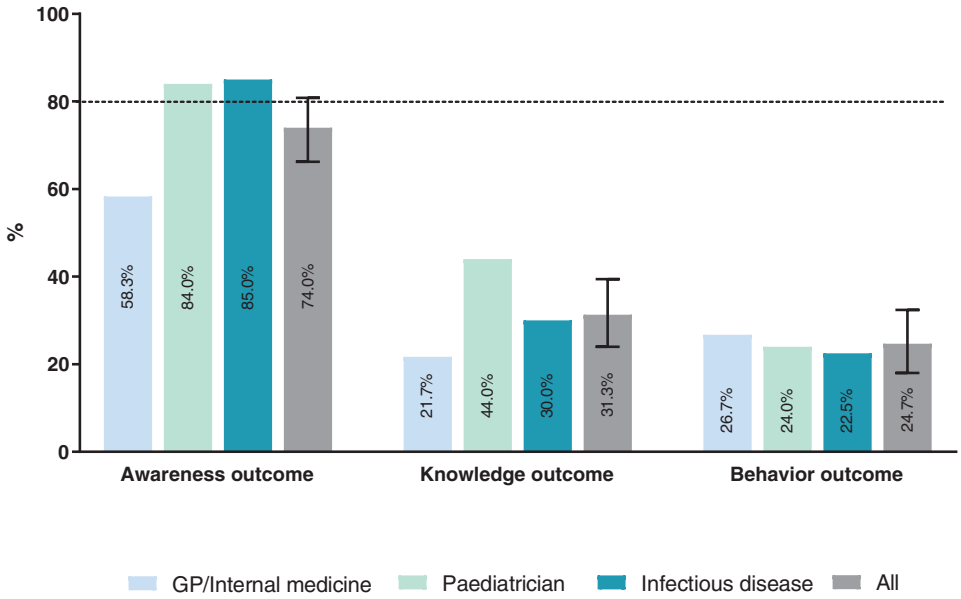


**FIGURE 2** Analysis of the three outcomes success criteria separately and per speciality in Thailand. Confidence intervals are presented as "whiskers" on the bar for "All" category. Criterion of success No 1: Awareness—Prescribers with at least 1 of 2 questions successfully answered. Criterion of success No 2: Knowledge—Prescribers with at least 3 of 4 questions successfully answered. Criterion of success No 3: Behaviour—Prescribers with the 2 questions successfully answered. Since these 3 criteria are independent, the total could exceed 100%. The threshold for considering each outcome successful was ≥80% of prescribers meeting the success conditions (dashed line).

defined as there was no *a priori* data to support a threshold in this context. This is a recognised challenge in the field.[12,13] In addition, there are plausible alternative explanations for the misalignment between participants' responses and the aRMMs, such as, other sources of information available to the prescribers and the healthcare practice context, which deserve further consideration.

Prescribers were generally aware that CYD-TDV was recommended in patients with PDI. In Brazil, which followed the prescreening vaccination strategy, prescribers seemed well aware that PDI should be confirmed before vaccination in all patients. However, only 11% considered that a confirmatory laboratory test was needed in all cases. A possible explanation could be the absence of reliable rapid diagnosis tests (RDTs) for confirmation of PDI during the period of this survey and few prescribers would have had access to reverse transcriptase-polymerase chain reaction (RT-PCR) or enzyme-linked immunosorbent assay (ELISA) tests, which require more time for processing and are expensive. The WHO has acknowledged this limitation and considered the development of RDTs for detection of PDI as a research priority.[6] In the absence of adequate tests, prescribers may have followed WHO population seroprevalence criteria; aggregate information about the location of the Brazilian participants suggested that 65% were from the Southeast region, a dengue endemic region. This may explain why a high proportion of prescribers also considered that CYD-TDV could be administered to travellers to endemic areas as they may have responded according to their local scenario. It is also possible that some considered CYD-TDV to be a travel vaccine, for example, similar to the yellow fever vaccine. Finally, the concept of "travel" may be differently perceived; for some it may be travel abroad, and for others it may be travel within the country.

In Thailand, which followed the population seroprevalence criteria, the guidelines are less prescriptive, so vaccination decisions rely more on clinical judgement of the benefit–risk for the individual. This may explain why approximately one fifth of prescribers also considered that CYD-TDV could be administered to individuals with no

PDI as they may have answered from the perspective of the adult population, which likely would have been exposed to dengue considering the high dengue endemicity in the country. Given that the aRMMs were issued by the PIDST and IDAT, more paediatricians and infectious disease specialists were informed about the CYD-TDV communications than GPs/internal medicine specialists as the latter may not regularly access the other medical societies websites. In addition, given that there were two waves of aRMM distribution in Thailand (the first communication immediately after WHO preliminary recommendations in September 2018, before the SAGE revised recommendations, and another in April 2019) may in part explain why some prescribers may have considered they were not informed about the updated label as they may no longer have considered this to be a recent update at the time of the survey. Although about 25% only prescribed before the release of the aRMMs, this did not impact the results as a comparison of responses from those who received and read the aRMMs with those who did not receive them showed similar success criteria between the two groups.

The survey also evaluated prescribers' adoption of dengue early warning signs as per the dengue case definition introduced by the WHO in 2009.[7] The results for both countries suggest that prescribers were more conservative in dengue monitoring by considering additional signs of dengue as early warning signs and not only those regarded as such by the guidelines. The usefulness of the revised dengue case classification has been debated. Despite being more sensitive for diagnosis of severe dengue and beneficial to triage and case management, dengue warning signs are considered by some as too broad and unspecific and would lead to an increase in the volume of patients requiring monitoring/hospitalisation. Overburdening the healthcare system may be a challenge in endemic countries where the volume of additional cases to monitor could strain limited healthcare resources.[14–16] This is particularly relevant in Thailand, where dengue management guidelines explicitly do not recommend the 2009 WHO dengue early warning signs guidelines. Thai specific guidance follows the 1997 WHO guideline, which emphasises monitoring of pathophysiological plasma leakage, considered to be more appropriate in dengue endemic countries.[17]

Since the development of this survey, a reliable point-of-care RDT has specifically been designed to identify individuals with PDI (Liberal et al. Unpublished results). The availability of reliable RDTs is expected to provide a predictive, measurable and practical method to determine PDI and facilitate the implementation of the pre-vaccination screening strategy. Therefore, the requirement to conduct pre-vaccination screening as a condition for vaccination has been strengthened in a proposal to update the prescribing information. The proposed revised document has been submitted to the Brazilian and Thai regulatory authorities. In Brazil, the prescriber aRMM will also be revised to reinforce the key safety messages. In addition, our study should also help inform the Thai Medical Societies responsible for the current aRMM in the country, as to how to improve the effectiveness of these materials, and whether additional medical societies should be involved to ensure GP/internal medicine specialists are also adequately informed. Future revised aRMMs will also emphasise the increased risk of severe and hospitalised dengue in vaccinated individuals not previously infected with dengue, given that only about half of the prescribers seemed to know this information. Indeed, the aRMMs will be revised based on the screen and vaccinate strategy with the use of reliable RDTs for detection of PDI and according to local authority recommendation. An endorsement of this strategy by the WHO and national health authorities, together with an effort to clarify dengue prevention and management guidelines, including the use of early warning signs, will contribute to the advancement of dengue management.

Our study has a number of limitations that may influence interpretation of the data. Although most of the questions assessed current knowledge or awareness of dengue vaccine prescription-related safety messages, some of the responses may be subject to recall bias, for example, if they received and read the aRMMs which could have underestimated awareness thus partially explaining the low result in Thailand. As with any survey, selection bias cannot be excluded given that participation was voluntary, so it is possible that participants may not be fully representative of all relevant prescribers in both countries. However the distribution of specialities in each country was compared between HCPs with complete questionnaires and those who were unreachable or refused to participate; there was a difference of less than 5% per strata which supports no relevant difference between participants and non-participants. In addition, another inherent limitation to surveys based on self-reported information is social desirability bias, where participants provide answers in a manner that will be viewed favourably by others. However, the use of pre-populated items in the questionnaire and the randomisation of the order of the items tends to reduce this bias.[18] The low response rates observed in our study are consistent with response rates observed in other physician surveys,[19,20] but concerns about bias maybe less of an issue than with general public surveys since physicians are more homogeneous as a group regarding knowledge, training, attitudes, and behaviour than the wider public.[21] To increase participation rates among the required specialists, several attempts were made to contact non-responders or those who refused initially, and optional compensation for the time spent with the survey was proposed. In addition, the challenges of implementing RMMs in an effective and consistent manner across countries with different healthcare systems make comparisons or generalisations between countries difficult. Thus, the data collected were highly heterogeneous which precluded combining the data from the two countries as initially planned.

In summary, our study provides valuable information regarding the effectiveness of the aRMMs used to inform prescribers about updated CYD-TDV indication and safety, as well as the hurdles impacting implementation of dengue vaccination. These results do not support that the aRMMs were effective as the success criteria were not met. In Brazil, awareness of the aRMM materials was successfully achieved but not for the knowledge and self-reported behaviour criteria, while in Thailand none of the criteria were successfully met. The availability of reliable RDTs for the detection of PDI together with clarification of dengue management guidelines and an update in the aRMMs will contribute to further advance dengue control.

## AUTHOR CONTRIBUTIONS

Mariana F. Almas, Massoud Toussi, Elisa Valero, Annick Moureau, and Lydie Marcelon contributed to the conceptual design of the study and/or data acquisition. All authors contributed to the interpretation of the data and participated in the drafting and critical revision of this report, approved the final version and are accountable for its accuracy and integrity. The authors would also like to acknowledge the contributions of: Laurence Serradell for input into the study design; Intissar Bourahla for project management; Anna Niedziółka for data acquisition; Aurélie Lampuré,for data analysis and interpretation; Stéphanie Meyer, Valentine Delore, Phatraporn Assawawongprom and Kelem Chagas for data interpretation; Shubhra Singh for medical writing of the study report; Marie-Caroline Guichard for study management; and Céline Zocchetti for project management, review of study protocol and report.

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## CONFLICT OF INTEREST

EV, AM and LM authors are employees of Sanofi Pasteur and may hold shares and/or stock options in the company. MFA and MT are employees of IQVIA who were contracted by Sanofi Pasteur to conduct this research.

## ETHICS STATEMENT

Ethical approval was not required to ascertain the effectiveness of the aRMMs in Brazil and Thailand. The study was conducted in accordance with all relevant regulatory requirements, including, the guidelines on good pharmacovigilance practices – post-authorisation safety studies good pharmacoepidemiology practice. The study was also performed according with the European Pharmaceutical Marketing Research Association (EphMRA) and European Society for Opinion and Marketing Research (ESOMAR) market research codes and guidelines.

## ENDNOTES

* Risk management plan details a set of activities and interventions designed to identify, characterise, prevent or minimise risks relating to the medicinal product, including the assessment of the effectiveness of those activities and interventions.

† Additional risk minimisation measures are interventions intended to prevent or reduce the occurrence of adverse outcomes associated with the exposure to a medicine beyond routine measures (the summary of product characteristics, the package leaflet, the labelling, the pack size, the legal status of the product, and its formulation). Educational programmes are aRMMs.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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