Calcium hydroxide + Clinoptilolite Larvicide for the Prevention of Dengue

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Section 1. Health problem and clinical management options

1.1. Overview and Burden of the Disease

What is Dengue?

Dengue is a mosquito-borne infection transmitted through bites of Aedes species (*Aedes aegypti* or *Aedes albopictus*) to humans. It is caused by the dengue virus with four serotypes (DENV 1,2,3, and 4), is most common in tropical and subtropical countries and is endemic in the Philippines. In 2023, the Philippines was the most affected country in the Western Pacific Region with an escalated dengue outbreak, reporting 167,355 cases and 575 deaths (CFR 0.34%) to the World Health Organization (WHO). Globally, the WHO attributed a moderate to low transmission and slight decrease of dengue cases in 2020-2022 due to COVID-19 pandemic and underreporting; but an increase in dengue cases has been observed in 2023. (WHO, 2023)

Dengue is commonly asymptomatic, but it can progress and manifest to severe flu-like symptoms or severe dengue that can be fatal. The 2009 WHO Dengue Case Classification stated that dengue severity can be divided into three: (1) probable dengue without warning signs, (2) dengue with warning signs, and (3) severe dengue fever. Warning signs manifest as abdominal pain, persistent vomiting, fluid accumulation, lethargy, and liver enlargement; while severe dengue fever progresses to plasma leakage, hemorrhage, and organ impairment (WHO, 2009). Secondary infection of dengue or individuals with current dengue infection and previously infected with another dengue serotype are likely to progress to severe dengue (Mizumoto et.al, 2014).

Disease Magnitude and Severity

A targeted search was conducted by three independent reviewers to detect local reports on the magnitude and severity of dengue cases in the Philippines. Local data on morbidity and mortality of dengue cases were all obtained from the DOH Epidemiology Bureau, and the Philippine Statistics Authority.

Local Morbidity Data

Dengue fever was the 8th, 10th, and 9th leading cause of morbidity in the Philippines in the years 2015, 2016, and 2018, respectively (Philippine Health Statistics, 2015, 2016, 2018). Meanwhile, the latest data on morbidity by the Department of Health in 2022 reported dengue fever as the 16th leading cause of morbidity for the overall population.

The DOH-Epidemiology Bureau (EB) through the Philippine Integrated Surveillance and Response - Epidemic-prone Disease Case Surveillance (PIDSR-EDCS) conducts surveillance of epidemic-prone potential diseases which includes dengue among others. These are captured on their sentinel and non-sentinel sites (PIDSR Annual Report, 2021). The PIDSR-EDCS releases a weekly surveillance report for reported suspect, probable, and confirmed dengue cases. Based on their data from 2019 to 2023, there was a dramatic decrease by 81.0% in reported cases from 2019 to 2020 as presented in Figure 1.1. According to the PIDSR Annual Report 2021, the decrease may be attributed to the COVID-19 pandemic. A decline in reported cases from

252,700 in 2022 to 195,603 in 2023 can also be observed, which may be due to an incomplete report in December 2023 at the time of review (DOH EB, 2023).

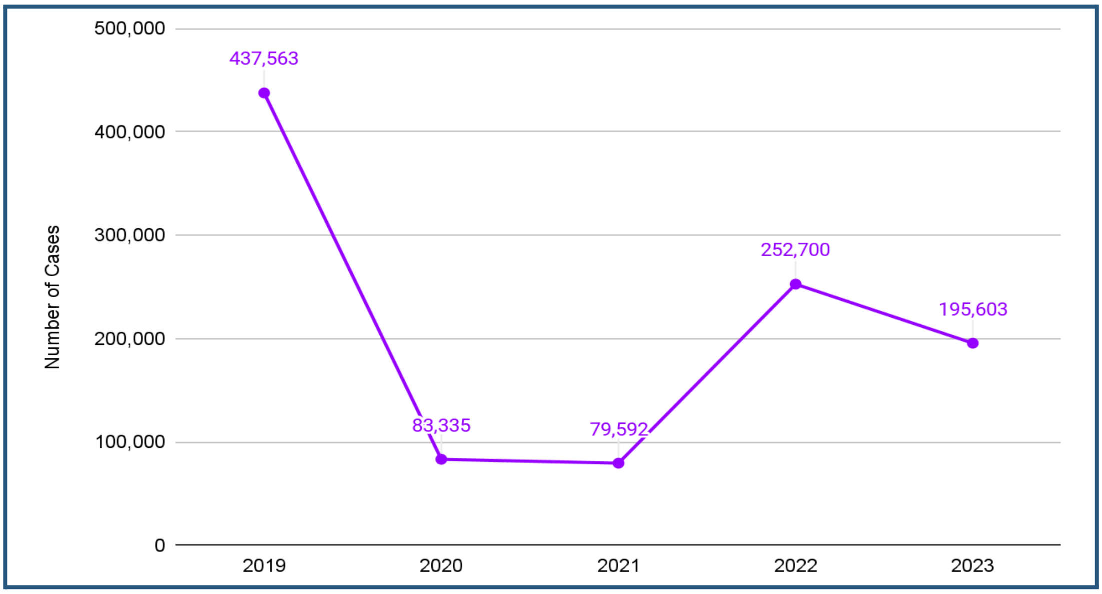

Figure 1.1. *Annual number of reported dengue cases in the Philippines from 2019 to 2023*

On the annual number of reported cases per region, Region III had the highest reported cases of dengue for 2021 and 2022 as shown in Figure 1.2. For 2023, NCR led the highest reported cases of dengue followed by Region III and CALABARZON.

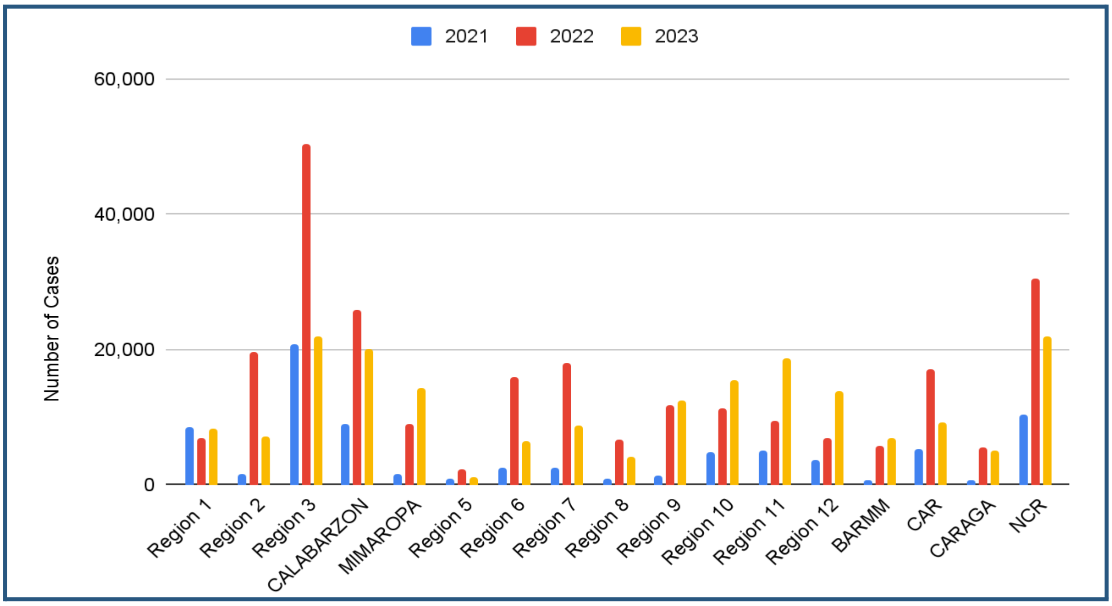

Figure 1.2. *Annual number of reported dengue cases in the Philippines per region from 2021 to 2023*

In terms of the incidence rates or the number of dengue cases per 100,000 population per region, Cordillera Administrative Region (CAR) had the highest incidence rate of dengue for the year 2022 and 2023 (DOH EB, 2023). This may be attributed to this region having the 2nd highest percentage of Geographically Isolated and Disadvantaged Areas (GIDA) Barangays in 2019 (DOH, 2019).

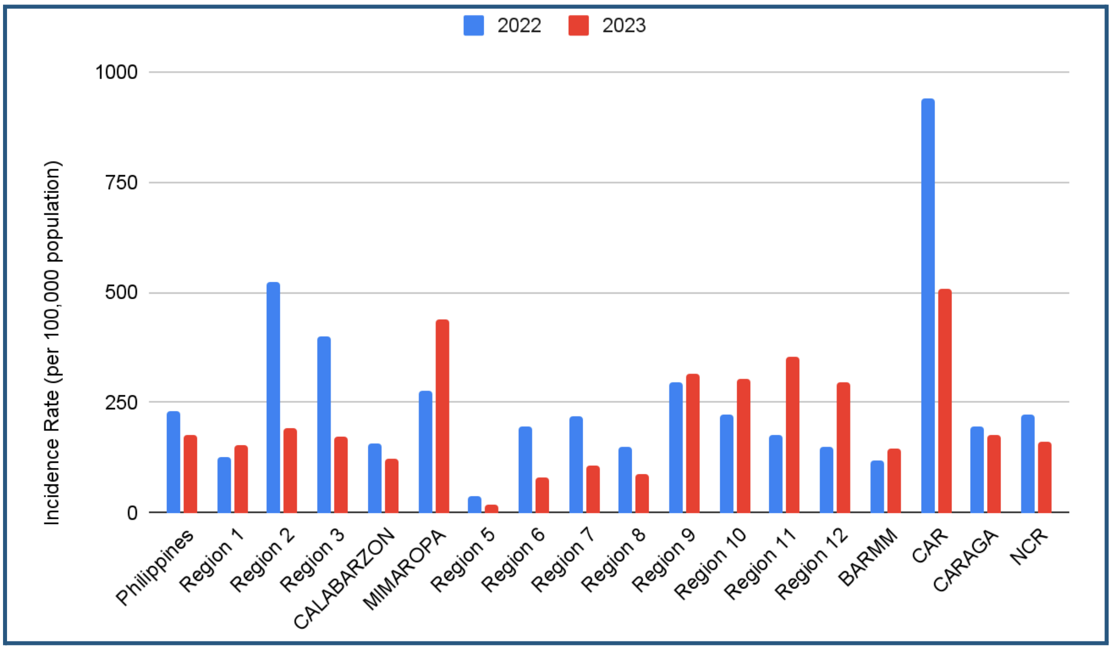

Figure 1.3. *Incidence rates of dengue (cases per 100,000 population) in the Philippines per region in 2022 and 2023*

In 2021, PIDSR reported that the most affected age group were those that belong to 10 to 14 years of age (15,209 or 19%) as shown in Figure 1.4. As for the sex distribution, males were shown to be more affected, comprising 54% of the total cases or 43,008 cases (PIDSR Annual Report, 2021).

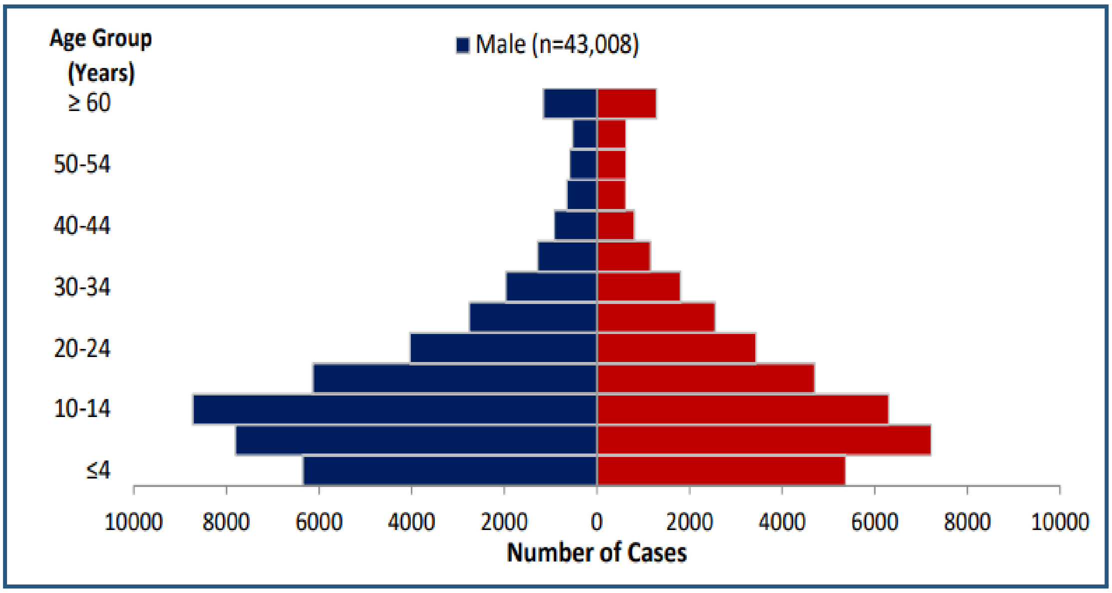

Figure 1.4. *Dengue cases reported by age group and sex in 2021*

Local Mortality Data

Dengue fever or classical dengue was the 9th and 4th leading cause of mortality in children aged 5-9 years old in 2015 and 2016, respectively. Meanwhile, the more severe type – dengue hemorrhagic fever was the 6th leading cause of mortality in children aged 1-4 years old in 2015 and 2016 while it was the 3rd in children aged 5-9 years old during the same period. Among adolescents aged 10-14 years, dengue hemorrhagic fever was the 8th and 7th leading cause of mortality in 2015 and 2016, respectively. However, in the overall Philippine population, dengue was not among the leading causes of mortality from 2015 to present (Philippine Health Statistics, 2015, 2016, 2017, 2018, 2019, 2020; Philippine Statistics Authority, 2021, 2022).

Based on the PIDSR-EDCS data from 2019 to 2023, a similar trend was observed on both dengue cases and deaths wherein there was a dramatic decrease by 80.8% in reported deaths from 2019 to 2020 as presented in Figure 1.5. There was also a slight decrease from 894 to 657 reported deaths from 2022 to 2023 which may be due to incomplete reported data at the time of review.

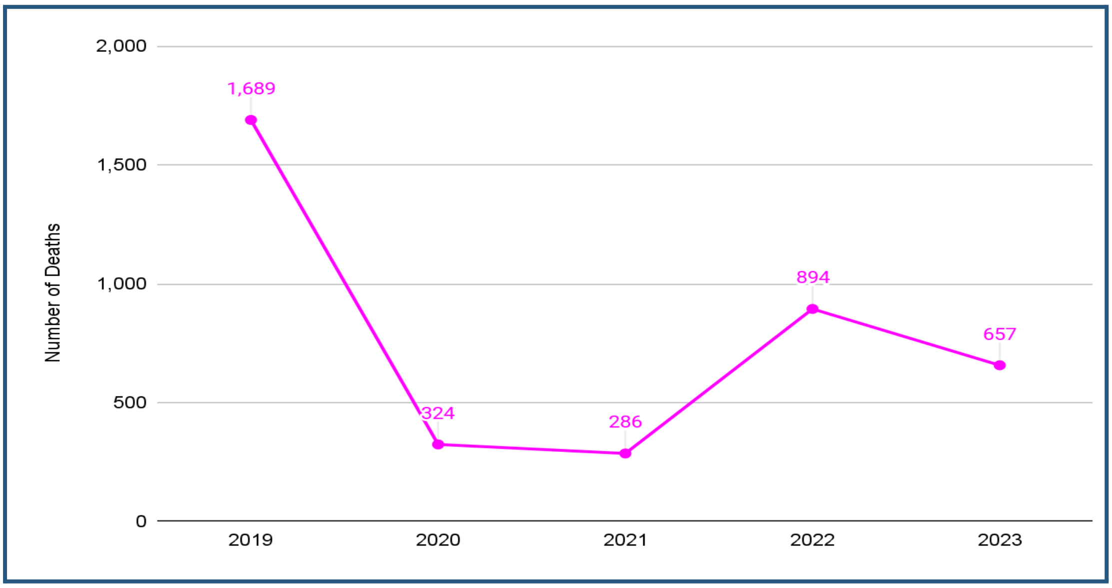

Figure 1.5. *Annual number of reported dengue deaths in the Philippines from 2019 to 2023*

As for the dengue deaths per region, Region III had the highest reported deaths from 2021 to 2022 while MIMAROPA leads for 2023 as shown in Figure 1.6.

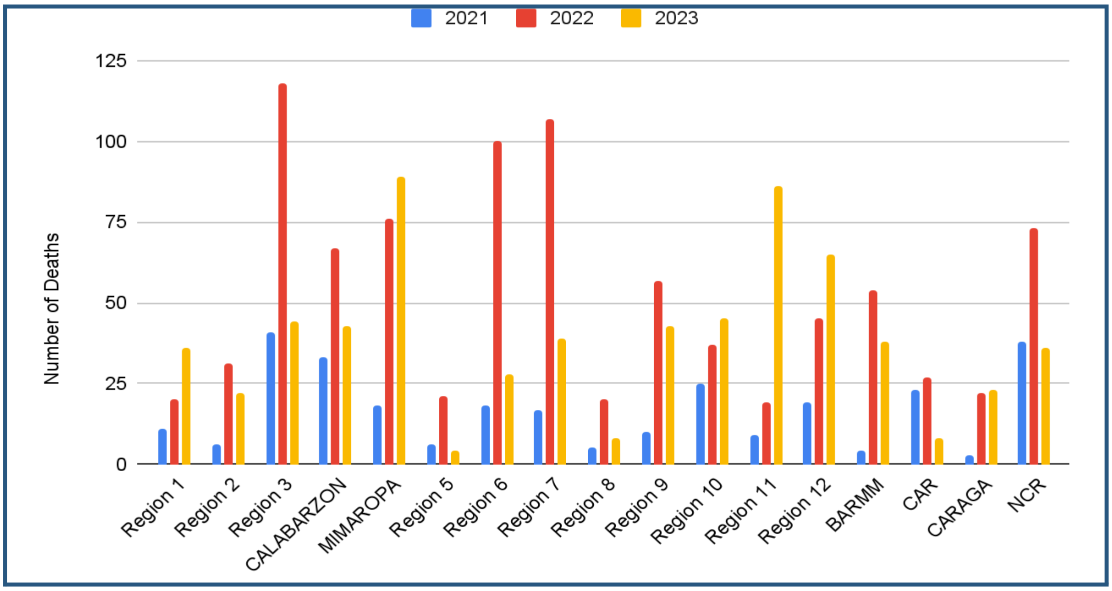

Figure 1.6. *Annual number of reported dengue deaths in the Philippines per region from 2021 to 2023*

In terms of annual dengue case fatality rate (CFR), the Philippines had a steady CFR of 0.40% from 2019 to 2021 as shown in Figure 1.7. After 2021, a decreasing trend can be observed from 0.40% to 0.34% in 2023. As for the annual CFR per region, MIMAROPA had the highest reported CFR for 2021 and 2023, and Region 5 for 2022 as shown in Figure 1.8.

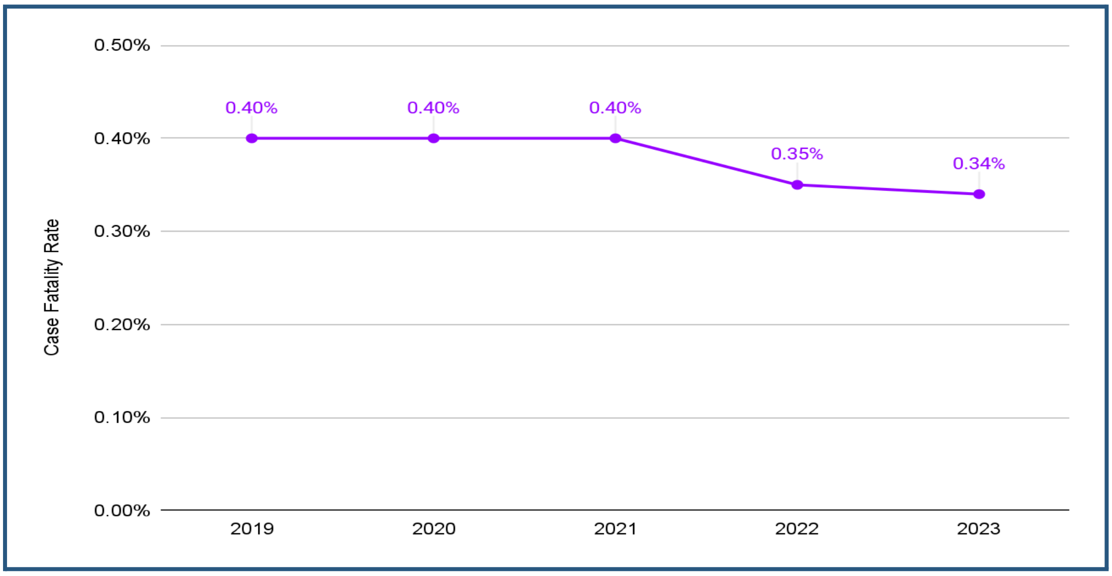

Figure 1.7. *Annual dengue case fatality rates in the Philippines from 2019 to 2023*

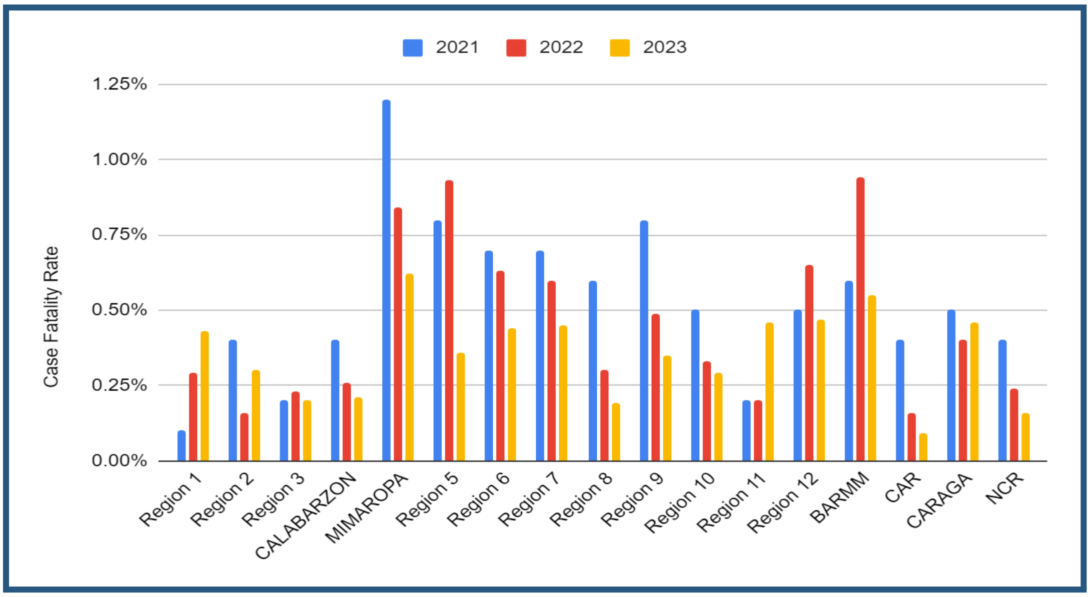

Figure 1.8. *Annual case fatality rates in the Philippines per region from 2021 to 2023*

1.2. Current management options

1.2.1. Local Clinical Practice Guidelines

Dengue Prevention

To combat the transmission of dengue and to control an outbreak, approaches focus on Integrated Vector Management (IVM), self-protection and environmental management. WHO also supports and promotes IVM as a complementary strategy to control transmission of dengue vectors (WHO, 2023). As vector controls including larvicides are health products and have been critical in preventing vector-borne diseases including dengue, WHO conducts a pre-qualification assessment process for vector control products (VCPs) that aims to increase access to safe, high-quality and effective VCPs, and to ensure that scarce resources available for disease control are used to maximum impact (WHO, 2021). Currently, the WHO has pre-qualified eight larvicides based on its active ingredients and synergist and these are: Temephos, Pirimiphos-methyl, PDMS (Polydimethylsiloxane), Diflubenzuron, Pyriproxyfen, Novaluron, Spinosad and *Bacillus sphaericus* and *Bacillus thuringiensis subsp*. Israelensis strain (WHO, 2023).

Standard of care for the management of dengue cases

The course of treatment for dengue focuses on management of symptoms and complications as there is “no direct antiviral therapy” against the dengue virus. Dengue has three phases of infection: febrile phase, a critical phase (plasma leakage), and a convalescent (reabsorption) or recovery phase (Thomas et.al, 2019; WHO, 2009).

The febrile phase of dengue shows symptoms of high fever and dehydration which usually lasts 2–7 days after which most patients recover without complications. It is often accompanied by facial flushing, skin erythema, generalized body ache, myalgia, arthralgia and headache. For patients that do not manifest warning signs and without comorbidities, it can be treated through outpatient management. It is recommended to monitor the manifestation of warning signs in patients and presence of comorbidities that may result in progression to severe dengue and other complications of dengue that require hospitalization and inpatient management. Dengue infection may develop to the critical phase characterized by plasma leakage that can lead to shock, severe hemorrhage, and organ impairment from prolonged shock. Lastly, in the convalescent or recovery phase, patients will recover from the critical phase throughand a gradual reabsorption of the extravascular compartment fluid. (WHO, 2009, Thomas et.al, 2019; Schaefer et.al, 2017, Pan American Health Organization, 2022).

In terms of prevention, there is currently no vaccine against dengue registered in the Philippines Food and Drug Administration (FDA). It can be noted however, that there have been developments and clinical trials for dengue vaccine. As of March 2024, there are two brands of attenuated dengue vaccine authorized in different countries (i.e., CYD-TDV (Dengvaxia®), TAK-003 (Qdenga®)) (Thomas, 2023; Thomas et.al, 2019). Dengue vaccine was added to the WHO Essential Medicines List (EML) for use in some high-risk populations in 2019. It can be noted that CYD-TDV (Dengvaxia®) is only indicated for persons with evidence of past dengue infection. Meanwhile, in November 2023, the WHO SAGE Strategic Advisory Group of Experts on Immunization recommended TAK-003 (Qdenga®) without limitations with regard to prior dengue infection but should be accompanied by a well-designed communication strategy and community engagement since it is yet to undertake post-marketing surveillance stage to address information gaps (WHO EML, 2023, WHO, 2023, PAHO, 2024).

1.2.2. Accessibility of treatment options (based on 5A's: Availability, Adequacy, Accessibility, Affordability, and Appropriateness)

Diagnosis and Case Management

In primary level and in instances of high cases or outbreak, Dengue fast lanes in Rural health units (RHUs) were established and activated to serve as triage areas for patients with signs and symptoms of dengue that will be subjected to Dengue Rapid Diagnostic Test, as per DOH Administrative Order 2016-0043 and DOH Department Memorandum 2015-0309 or the Reactivation of Dengue Fast Lanes and Continuing Improvement of Systems for Dengue Case Management and Services**.** Dengue Centers of Excellence (COE) through Tertiary hospitals are also established through DOH Administrative Order 2020-0009. It aims to "improve the [clinical] management of Dengue in terms of absorptive capacity, equipment and human resource" and "complement the vector control and health promotion" (p. 1-2) measures. This Order enables listed Tertiary hospitals to serve as National Referral Hospital and to operate a Dengue Specialized Unit (DSU) for dengue WITH warning signs, Dengue WITHOUT warning signs, Severe Dengue and Dengue-related cases.

Integrated Vector Management

Since 1998, the month of June has been the National Dengue Awareness Month in the country by Proclamation No. 1204 for the prevention and control of dengue. In 2001, as per DOH Administrative Order (AO) No. 45, 2001 or the '*Guidelines on the Application of Larvicides on the Breeding Sites*', *Temephos* is the recommended insecticide for larvae control due to its low effective dosage. The Revised Criteria for the Selection of Pesticides Used in IVM or Administrative Order No. 2022-0026 was released in 2022. It removes the WHO Prequalification in the use of insecticides and larvicides in IVM control of vector-borne diseases. It instead provides guidance and enumerates the criteria or technical specification for the selection of larvicide used in IVM control for concerned agencies.

In 2018, DOH launched the nationwide campaign and implementation of the Enhanced 4-S Strategy as prevention control and control strategy against Dengue, Chikungunya and Zika, through AO No. 2018- 0021. Enhanced 4-S campaign focuses on the integrated community efforts to combat dengue with these four steps: (1) "4-o'clock habit" afternoon to Search and destroy mosquito breeding sites; (2) Secure self-protection from mosquito bite; (3) Seek early consultation; and (4) Support fogging/spraying only in hotspot areas where there is increase in cases. In instances of increasing dengue cases or dengue outbreak, DOH relaunches and intensifies the campaign of practicing Enhanced 4-S.

1.2.3. Existing government policy and reimbursement mechanism

With the burden of dengue cases in the Philippines, the Department of Health (DOH) introduced the National Dengue Prevention and Control Program in 1993. It aims to reduce the burden of dengue disease and achieve a dengue-free Philippines. The program components are: Surveillance, Case Management and Diagnosis, Integrated Vector Management, Outbreak Response, Health Promotion and Advocacy, and Research. (Cordero, 2024) In terms of reimbursement mechanisms for dengue cases, PhilHealth Case Rates are available for different classification of inpatient dengue cases. Dengue without warning signs [ICD A97.0] and Dengue with warning signs [ICD A97.1], has a case rate of Php 10,000, while Severe Dengue [ICD A97.2] has a case rate of Php 16,000.

Section 2. Description, technical characteristics, and use of the health technologies

2.1 Proposed intervention

Calcium hydroxide + Clinoptilolite *(Kiti-KitiX)* larvicide is intended to be used as a prevention control larvicide in liquid form against mosquito larvae or immature mosquitos *(Aedes aegypti)*. Based on the submitted dossier, this Filipino invention claims to be effective in terminating the early life cycle of mosquitoes thereby preventing them from further multiplying and spreading dengue. It will serve as larvae traps, targeting locations, containers, or stagnant water that serve as breeding places of immature mosquito larvaes, such as household and community-based targeting.

Based on the submitted dossier, the product formulation includes calcium hydroxide which has larvicidal effects on mosquitoes and an additive clinoptilolite which absorbs calcium ions thus possibly causing higher lethal concentrations for the mosquito pupae.

The inventor estimated that one bag application of Calcium hydroxide + Clinoptilolite *(Kiti-KitiX)* can cover 30-60 households or 150-300 people that should be applied every 11 months by Barangay Health Workers and Environmental and Sanitary Officers.

2.2. Comparator/s

The DOH Disease Prevention and Control Program (DPCB) recommended **previously utilized larvicides (i.e., Temephos, Pyriproxyfen, Novaluron) and other larvicides indicated in AO 2022-0026)** as comparators for this review.

In 2001, Temephos, an organophosphate, was the larvicide recommended by the DOH and WHO to use during the beginning of the dengue season and repeated every 5 weeks as stated in the DOH Administrative Order No. 45, 2001. Other previously utilized larvicides by the DOH are Pyriproxyfen and Novaluron which are both pre-qualified by WHO.

In 2022, the DOH revised the criteria for the selection of pesticides used in the IVM program through Administrative Order No. 2022–0026. It removed the WHO prequalification of larvicides and enumerates criteria for the selection of pesticides (e.g. formulation of larvicides) in IVM program, promoting cost-effectiveness, efficiency, and public health safety in the procurement process for program implementers, other health personnel, and LGUs.

The **Enhanced 4-S strategy** launched through DOH AO 2018-0021 being implemented nationwide was added as a comparator of interest by the HTA Council. It is a strategy in vector control measures, by promoting a 4 o'clock habit of searching and destroying breedings sites. Enumerated below is what the enhanced 4-s strategy stands for:

1. Search and destroy mosquito breeding sites
2. Secure self-protection from the bites of mosquitoes
3. Seek early consultation
4. Support fogging/spraying only in hotspot areas where increase in cases is registered for two consecutive weeks to prevent an impending outbreak

Section 3. Objectives and Research Questions

3.1.Objectives

Policy Question
Should the Calcium hydroxide + Clinoptilolite *(Kiti-KitiX)* larvicide be funded by the Department of Health (DOH) for the prevention of Dengue?

Research Questions (RQ)

1. Responsiveness to Magnitude and Severity

   What is the magnitude and severity of dengue in the Philippines? Is dengue a public health priority?

2. Clinical efficacy, effectiveness and safety

   2.1. Is the Calcium hydroxide + Clinoptilolite *(Kiti-KitiX)* larvicide efficacious/effective vs. previously utilized larvicides by DOH and enhanced '4S' strategy in controlling the spread of dengue in terms of population-level reduction in i) total dengue cases, ii) severe dengue cases, and iii) mortality due to dengue?

   2.2. Is the Calcium hydroxide + Clinoptilolite *(Kiti-KitiX)* larvicide safe for use vs. previously utilized larvicides by DOH and enhanced '4S' strategy in terms of any harmful effects in environmental and human health?

   2.3. What are the current recommendations from country guidelines on the use of Kiti-KitiX against dengue?

3.2. PICO (Population, Intervention, Comparator, Outcomes) of the Research Question

Population	Entire Population, Filipino communities
Intervention	Calcium Hydroxide and Clinoptilolite *(Kiti-KitiX)* as a mosquito larvicide for vector control for the prevention of Dengue dependent on population density: 1 bag (25kg) for 150-300 people
Comparator	Previously utilized products: Temephos, Pyriproxyfen, Novaluron, Other larvicides (AO 2022-0026) Enhanced 4S Strategy (AO 2018-0021): Search and Destroy Breeding Site, Seek Early Consultation, Self Protection Measures, Say yes to fogging only during outbreaks
Outcomes	Efficacy/Effectiveness: - Population level reduction in dengue cases: Total dengue cases (any severity) Severe dengue cases Mortality due to dengue Safety - Any harmful effects (environmental and human health)

Section 4. Methodology of the Clinical Assessment

For the assessment of the clinical efficacy, effectiveness, and safety of calcium hydroxide + clinoptilolite *(Kiti-KitiX)*, relevant evidence from systematic searches, company submissions, and data requests from the Philippine FDA and several content experts were examined.

4.1. Location and Selection of Studies

4.1.1. Systematic review

A systematic search was performed from three databases, namely, PubMed, Acta Medica, and HERDIN. No restrictions were applied on publication date, language, and study design were applied in the systematic search. This search was conducted on 10 January 2024 using the following search strategies:

1. *(calcium hydroxide) AND (dengue)*
2. *(clinoptilolite) AND (dengue)*
3. *(calcium hydroxide AND clinoptilolite) OR Kiti-KitiX*
4. *(calcium hydroxide AND dengue) OR (calcium hydroxide AND larvae) OR (calcium hydroxide AND mosquito) OR (calcium hydroxide AND vector) OR (calcium hydroxide AND aedes)*
5. *(clinoptilolite AND dengue) OR (clinoptilolite AND larvae) OR (clinoptilolite AND mosquito) OR (clinoptilolite AND vector) OR (clinoptilolite AND aedes)*

Due to limited studies detected, an additional systematic search was done on 01 February, 2024 using following search terms in the three databases mentioned above and Google Scholar:

6. *(calcium hydroxide OR clinoptilolite)*
7. *(calcium hydroxide OR clinoptilolite) AND (safety)*

Title and abstract screening were conducted by two independent reviewers using the inclusion criteria indicated in Table 4.1 below. Any disagreements were settled with a third reviewer when needed. Due to the scarcity of studies detected, studies on the individual components of *Kiti-KitiX* were added in the intervention of interest of the inclusion criteria.

Table 4.1. *Inclusion Criteria based on the PICO of the review*

	Inclusion Criteria
Population	Entire Population, Filipino communities
Intervention	- Calcium Hydroxide and Clinoptilolite *(Kiti-KitiX)* as a mosquito larvicide for vector control for the prevention of Dengue dependent on population density: 1 bag (25kg) for 150-300 people - Calcium Hydroxide - Clinoptilolite
Comparator	Previously utilized products: Temephos, Pyriproxyfen, Novaluron, Other larvicides (AO 2022-0026)

	Enhanced 4S Strategy (AO 2018-0021): Search and Destroy Breeding Site, Seek Early Consultation, Self Protection Measures, Say yes to fogging only during outbreaks
Outcomes	Efficacy/Effectiveness: - Population level reduction in dengue cases: Total dengue cases (any severity) Severe dengue cases Mortality due to dengue Safety - Any harmful effects (environmental and human health)

A total of 126,154 studies were identified from the systematic searches. Only 179 studies were subjected to title and abstract screening. The very high yield from Google Scholar for search strings no. 6 and 7 and PubMed using search string no. 6 were not subjected to title and abstract screening due to the voluminous literature considering the time constraints.

Of the 179 studies, only four studies on the safety of clinoptilolite were included after title and abstract screening. However, these were ultimately excluded after full text screening because the formulation of the interventions may be different compared to what was used in the larvicide. Other studies were excluded due to wrong PICO and study design. Majority of which are not clinical studies. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for the retrieval of efficacy/effectiveness and safety studies is presented in Figure 4.1 below. The list of studies detected from the systematic search that underwent title and abstract screening and their reasons for exclusion is listed in Annex A.

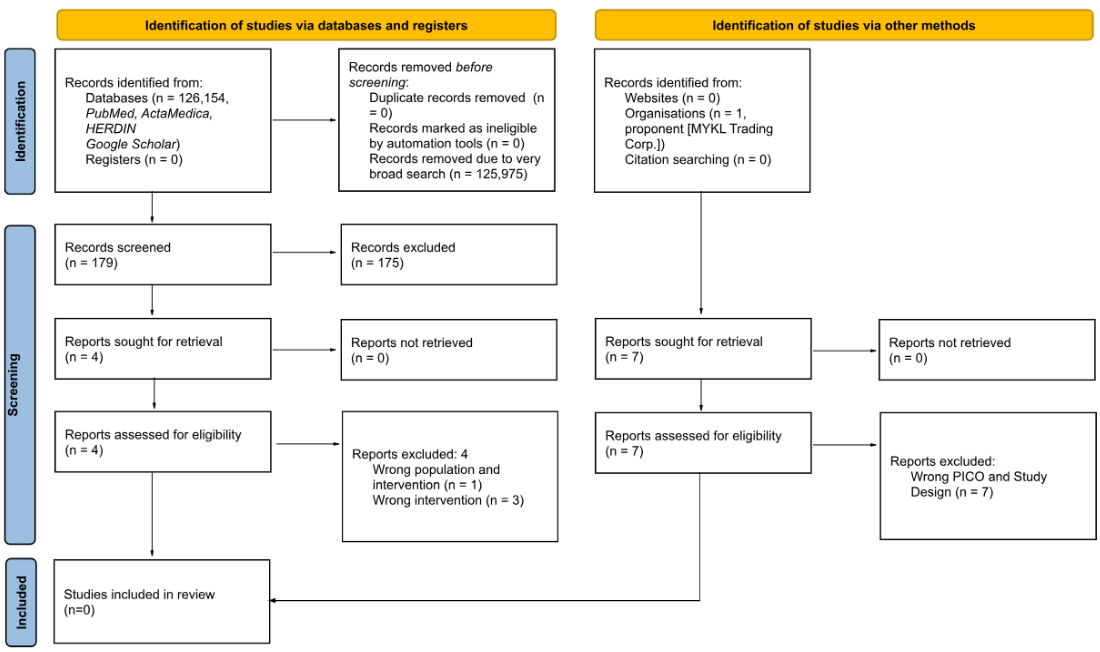

Figure 4.1. *PRISMA flow diagram of studies detected in the systematic search*

4.1.2. Proponent Submissions

Five studies submitted in the proponent's nomination dossier were all subjected to full-text screening by two independent reviewers using the inclusion criteria in Table 4.1. A third reviewer was consulted to settle disagreements until a consensus was reached.

None of these submissions were included in the review since one study did not provide methodology and the other four studies are unpublished documents and did not match the PICO question. All studies were also not clinical studies, but evaluated the larvicidal activity of calcium hydroxide + clinoptilolite *(Kiti-KitiX)* against *Aedes Aegypti* through field simulation or evaluation which does not match the outcomes of interest in this review.

To supplement the review, additional evidence was requested from the proponent on the safety, toxicity, and other precautions that should be noted upon exposure, use or disposal of the larvicide. Ten documents were received including one Material Safety Data Sheet (MSDS), two animal studies, four certifications from local government health offices, one certification from a University, one certification from a local animal farm, and one laboratory experiment result from the Department of Agriculture. The two animal studies submitted by the proponent were subjected to full-text review but were excluded since both did not cover the outcomes of interest of this review. (Note: Only the animal studies were included in the PRISMA diagram. Other types of documents (e.g., certifications, laboratory results) were not included in the PRISMA count.)

The characteristics and reasons for exclusion of the seven studies submitted by the proponent are shown in Annex B. Other documents submitted by the proponent were also screened as potential supplementary evidence but were ultimately excluded in the review due to lack of supporting studies.

4.1.3. Philippine FDA Documents

The studies submitted by the marketing authorization holder that were used by the Philippine FDA in the efficacy/effectiveness evaluation for the authorization of calcium hydroxide + clinoptilolite *(Kiti-KitiX)* were also requested. Unfortunately, access to these data was not possible due to confidentiality concerns. Hence, a consultation meeting with the FDA Center for Cosmetics and Household/Urban Hazardous Substances Regulation and Research (CCHUHSRR) was held instead to seek clarification on the process of authorization.

A consultation meeting with FDA CCHUHSRR provided valuable insights into the registration process for the Kiti-KitiX larvicide. According to the FDA, the initial approval in 2009 submission and two subsequent renewals (second and third approval) in 2011 and 2014 of the Certification of Product Registration (CPR) of Kiti-KitiX larvicide adhered to the guidelines outlined in Administrative Order (AO) 303 issued in 1976, while the third renewal (fourth approval) in 2019 followed the AO 2014-0038 guidelines and list of requirements. The FDA acknowledged that the product passed the evaluation criteria stipulated in these Administrative Orders. However, it can be noted that both AOs did not include Human Exposure Safety Data and Environmental Data in the evaluation criteria.

The FDA emphasized that the forthcoming renewal process shall adhere to the updated guidelines stipulated in AO 2019-0008, which now encompass Human Exposure Safety Data and Environmental Data within the evaluation criteria. The CPR for the product is set to expire on April 17, 2024. For reference, see Annex C for the list of requirements and guidelines stipulated in the Administrative Orders mentioned.

4.1.4. Consultations with other agencies

Given the limited evidence available, the reviewers reached out to five additional agencies: the University of the Philippines National Poison Management and Control Center (UP NPMCC), UP Manila College of Public Health Department of Environmental and Occupational Health (UPM-CPH-DEOH), Department of Energy and Natural Resources Environmental Management Bureau (DENR-EMB), UP Diliman Natural Sciences Research Institute (UPD-NSRI), and UP Diliman Institute of Environmental Science and Meteorology (UPD-IESM). These consultations aimed to gather more comprehensive data on the human and environmental safety profile of the product.

Upon the suggestion of HTA Council, UP NPMCC was consulted on the safety, acceptable amounts, toxicity levels, and other precautions that should be noted upon exposure, use, or disposal of the following components present in the Kiti-KitiX larvicide - (1) 80% Calcium hydroxide + 20% Clinoptilolite, (2) Calcium hydroxide, and (3) Clinoptilolite. The UP NPMCC then recommended to consult the UPM-CPH-DEOH and DENR-EMB on the environmental impact (e.g., environmental fate, aquatic and soil toxicity, environmental persistence) and other precautions that should be noted upon exposure or disposal of the *Kiti-KitiX* larvicide and its individual components. While the UPM-CPH-DEOH recommended consulting the UPD-NSRI and UPD-IESM on the environmental impact of *Kiti-KitiX* larvicide and its individual components.

4.2. Data Extraction

After full-text screening of studies acquired from different sources, no studies were included in this review. Hence, data extraction was not applicable.

4.3. Critical Appraisal

Critical appraisal was not performed since all of the studies detected were excluded from this review.

4.4. Data synthesis

Only two expert statements were ultimately included in the review. These include statements from National Poison Management and Control Center (NPMCC) on Kiti-KitiX individual components' effect on humans, and UP Manila College of Public Health Department of Environmental and Occupational Health (UPM-CPH-DEOH) on environmental impact.

Section 5. Results of Synthesis of Clinical Evidence

5.1. Study Characteristics

5.1.1. Efficacy/Effectiveness

There was no available clinical evidence detected that reported the efficacy or effectiveness of the Calcium hydroxide + Clinoptilolite *(Kiti-KitiX)* larvicide in reducing dengue cases, severe dengue cases and deaths due to dengue. All studies detected evaluated the larvicidal activity of calcium hydroxide + clinoptilolite *(Kiti-KitiX)* against *Aedes Aegypti* through field simulation or evaluation which does not match the outcomes of interest in this review.

5.1.2. Safety

No clinical evidence that reported the safety of the Calcium hydroxide + Clinoptilolite *(Kiti-KitiX)* as larvicide in human exposure and environmental impact was included. Further, there was also no clinical evidence included on the individual components of the larvicide. Expert statements from UP NPMCC based on animal studies and available Material Safety Data Sheet (MSDS) from the United States Center for Disease Control, National Institution for Occupational Safety and Health (US CDC NIOSH) and PubChem, and UPM-CPH-DEOH based on literature review were the only evidence for safety included in this review.

5.2. Results of Synthesis

5.2.1. Efficacy/Effectiveness

There was no available clinical evidence detected that reported the efficacy or effectiveness of the Calcium hydroxide + Clinoptilolite *(Kiti-KitiX)* larvicide in reducing dengue cases, severe dengue cases and deaths due to dengue.

5.2.2. Safety

The safety results for clinoptilolite in this review are categorized into two: 1) human and animal exposure, and 2) environmental exposure.

A. Human and Animal Exposure

The UP NPMCC conducted a comprehensive literature review on the animal and human toxicity studies of Calcium hydroxide + Clinoptilolite larvicide *(Kiti-KitiX)* and found no studies. However, only animal studies and MSDS from US CDC NIOSH and PubChem were found for its individual components. According to the toxicological results, both acute and chronic usage of *Kiti-KitiX*'s individual components would have corrosive or caustic effects, and each component appears to have toxic effects that are dose-dependent. UP NPMCC recommended to consult other appropriate agencies with regards to the environment impact use and disposal of *Kiti-KitiX*. The results of the evidence synthesis by the UP NPMCC may be provided upon request to the HTA Philippines and the UP NPMCC.

B. Environmental Exposure

Upon consultation with UPM-CPH-DEOH, it was stated that there is currently no retrievable information on Calcium hydroxide + Clinoptilolite larvicide *(Kiti-KitiX)* since this is a patented product. A rapid literature review was also conducted on its individual components and has revealed that for calcium hydroxide, high concentrations have been noted to elevate water alkalinity that may possibly affect aquatic ecosystems by exceeding pH levels tolerable for certain species. As for Clinoptilolite, it may release specific ions into the environment that may adversely affect aquatic ecosystems depending on its nature and concentration. Aquatic organisms may suffer disturbances in their physiological processes, which could have a negative impact on their development, reproduction, or survival, depending on the kind and amount of ions discharged.

Section 6. Review of Guideline Recommendations

6.1. Methodology

A total of 20 international agencies, national regulatory authorities (NRAs) and ministries of health (MOH) websites were searched for the guideline recommendations on Calcium Hydroxide + Clinoptilolite larvicide and the use of larvicides in general. This search included the World Health Organization (WHO), nine agencies from Asian countries (i.e., Singapore National Environmental Agency (NEA), Malaysia Health Technology Assessment Section (MaHTAS), Indonesia MOH, Thailand MOH, Vietnam MOH, Japan MOH, Labor and Welfare (MHLW), China Center for Disease Control (CDC), Nepal MOH, India MOH), five agencies from Latin America (i.e., Mexico Secretariat of Health, Brazil MOH, Colombia Ministry of Health and Social Protection, Paraguay Ministry of Public Health and Social Welfare, Peru MOH), United States Center for Disease Control (US CDC), United Kingdom (UK) National Health Services (NHS), European Health Union, Public Health Agency of Canada, and Center for Disease Network Australia (CDNA). According to the WHO, the Americas, South-East Asia and Western Pacific regions are the most seriously affected, with Asia representing around 70% of the global disease burden of dengue. Hence, these countries were included in the search for guidelines. The search was conducted on 17 January 2024. The summary of recommendations and guidelines are detailed in Table 6.1.

6.2. Results

Of the 20 agencies scoped, twelve had explicitly recommended the use of larvicides in their guidelines. However, none of which mentioned the use of Calcium Hydroxide + Clinoptilolite or its individual components as a larvicide. Three countries (i.e., Nepal MOH, Colombia Ministry of Health and Social Protection, and Mexico Secretariat of Health) specifically recommended the use of WHO prequalified list of larvicides to which calcium hydroxide, clinoptilolite, or their combination are not listed. It can also be noted that all Latin American countries explicitly recommended the use of larvicides, while only two countries from Southeast Asia (i.e., Singapore, Malaysia) explicitly recommended the use of larvicides.

Table 6.1. Review of guideline recommendations on the use of larvicides

Agency	**Date of Recommendation** *Reference Article/Document*	**Recommends the use of Larvicides?**	**Recommends the use of *$Ca(OH)_2$ + Clinoptilolite (Kiti-KitiX)* ?**
World Health Organization (WHO)	17 March 2023 *Fact Sheet*	No mention of larvicides	No mention of specific larvicides
	2017-2018 *Vector Control Products*	Yes, with WHO Prequalified Larvicides *(See Annex D)*	No
Asian Countries			
Singapore NEA	2020 *Why does NEA use the same strategies that yield the same results to tackle dengue year after year?*	Yes	No mention of specific larvicides
Malaysia HTAS	2019 *HTA Report: Integrated Vector Management (IVM)*	Yes, IVM also involves initiating control measures such as larvicide treatment before vector season starts.	No mention of specific larvicides
Indonesia MOH	2021 *MANAGEMENT OF DENGUE INFECTION IN CHILDREN AND ADOLESCENTS*	No mention of larvicides	No mention of specific larvicides
Thailand MOH	No data; Website inaccessible		
Vietnam MOH	2023 *DIAGNOSIS AND TREATMENT OF DENGUE HEMORRHAGIC FEVER (Translated via Google)*	No mention of larvicides	No mention of specific larvicides
Japan MHLW	2023 *About Dengue Infection (Translated via Google)*	No mention of larvicides	No mention of specific larvicides
China CDC	No data found (https://en.chinacdc.cn/)		
Nepal MOH	2019 *National Guidelines on Prevention, Management and Control of Dengue in Nepal*	Yes	No, *only Temephos, BTI, Methoprene, Pyriproxyfen, Pirimiphos-methyl, Diflubenzuron, Novaluron, Pyriproxyfene, and spinosad*
India Ministry of Health and Welfare	N.d. *Vector Control Measures*	Yes	No mention of specific larvicides
Latin American Countries			
Brazil MOH	2023 *MOH reinforces guidelines to combat dengue in homes*	Yes	No mention of specific larvicides

	(Translated via Google)		
Colombia Ministry of Health and Social Protection	N.d. *Management for Surveillance Entomology and Control of Dengue Transmission* *(Translated via Google)*	Yes	No, *only Temephos, BTI, Diflubenzuron, and Pyriproxyfen*
Mexico Secretariat of Health	2020 *Methodological Guide for Larval Control Actions* *(Translated via Google)*	Yes	No, *only Temephos, BTI, Spinosad, Methoprene, Novaluron, and Pyriproxyfen*
Paraguay Ministry of Public Health and Social Welfare	2022 *National Disease Surveillance and Control Guide* *(Translated via Google)*	Yes	No mention of specific larvicides
Peru MOH	2024 *Dengue: what are breeding sites* *(Translated via Google)*	Yes	No mention of specific larvicides
Other Countries			
US CDC	2020 *Larvicides*	Yes	No mention of specific larvicides
UK NHS	2023 *Dengue*	No mention of larvicides	No mention of specific larvicides
European Health Union	2014 *Guidelines for the surveillance of invasive mosquitoes in Europe*	No mention of larvicides	No mention of specific larvicides
Public Health Canada	2023 *Dengue Control*	No mention of larvicides	No mention of specific larvicides
Center for Disease Network Australia	2015 (current as of 2022) *National Guidelines for Public Health Units*	Yes	No mention of specific larvicides

Section 7. Discussion and Conclusion

7.1. Discussion of Results

Unpublished field experiments submitted by the proponent suggest that using Calcium Hydroxide + Clinoptilolite *(Kiti-KitiX)* is effective in dengue control with 30-100% larval mortality against *A. aegypti* (Ebol, 2013 [unpublished], Salazar, 2009 [unpublished]).

In terms of the clinical efficacy/effectiveness of the larvicide, there was no clinical evidence available vs. previously utilized larvicides by the DOH and enhanced '4S' strategy in reducing dengue cases, severe dengue cases and deaths due to dengue.

In terms of safety of Calcium hydroxide + Clinoptilolite *(Kiti-KitiX),* there was also no clinical evidence found in this review. Further, individual components of the larvicide were also investigated. However, no study was detected on the safety of Calcium Hydroxide. Meanwhile, for Clinoptilolite, studies detected were excluded due to differences in the formulation and use of the intervention (i.e., studies detected used clinoptilolite as a food supplement and for topical administration).

The reviewers also consulted experts on the safety of the product because of the limited result of the systematic search. Overall, only two institutions responded. The UP NPMCC concluded that both acute and chronic usage of Kiti-KitiX's individual components would have corrosive or caustic effects, and each component appears to have toxic effects that are dose-dependent on humans based on animal studies and MSDS from US CDC NIOSH and PubChem. The institution also recommended consulting other agencies for the environmental impact of the product.

From the agencies consulted for environmental impact, only the UPM-CPH-DEOH responded wherein they concluded that high concentrations of calcium hydroxide have been noted to elevate water alkalinity, potentially affecting aquatic ecosystems by exceeding pH levels, tolerable for certain species while clinoptilolite may adversely affect aquatic ecosystems through ion exchange based on rapid literature review.

Additionally, guidelines review was conducted wherein 20 agencies were scoped however none mentioned the use of Calcium Hydroxide + Clinoptilolite or its individual components as larvicide.

Lastly, it was noted that the CPR for this product has already expired last 17 April 2024. In addition, upon consultation with FDA, no human exposure safety data and environmental data were considered on the previous authorization of the product but will be included based on the Administrative Order 2019-0008 upon the next renewal of CPR.

7.2. Limitations of Evidence

The limited number of available studies was considered as the biggest limitation of this review. Despite broadening the inclusion criteria and seeking additional evidence from the proponent, Philippine FDA, and five other institutions, only two statements from consulted experts on safety of the individual components of the larvicide were included, and no studies were detected on efficacy/effectiveness.

An overall lack of clinical studies was also noted. All efficacy/effectiveness studies on the *Kiti-KitiX* larvicide evaluated larvicidal activity through laboratory experiments and field evaluation which does not match outcomes of interest of this HTA review which aims to measure patient or population level outcomes. The literature review conducted by the UP NPMCC and UPM-CPH-DEOH also only detected animal studies and MSDS from international institutions. Furthermore, there was a lack of published studies as the studies submitted by the proponent were not published in peer-reviewed journals. Additionally, the requirements used in the CPR approvals of the Philippine FDA for this product were not obtained due to data confidentiality concerns

To add, human and environmental safety data requested by the HTA Council to the Philippine FDA did not correspond to the requirements of the previous CPR approvals of the *Kiti-KitiX* larvicide. The reviewers anticipated these data to be available prior to the CPR expiration since these are now part of the requirement of the updated guidelines stipulated in the FDA's AO 2019-0008. However, these were not obtained and the CPR renewal application process extended to a 120 days grace period.

7.3. Limitations of the review process

The outcomes of interest of this HTA review aimed to measure clinical outcomes and its epidemiological impact in accordance with the current Philippine HTA Methods Guide. This is in contrast with the evidence requirement of the Philippine FDA on assay procedure of the active component, bio-efficacy, and toxicity used in previous CPR approvals which were approved using studies that measure larval mortality based on FDA AO 303 issued in 1976 and FDA AO 2014-0038. This limitation may be addressed as well by the health technology-specific methods guides (MG) on preventive and promotive health (PPH) being developed by HTA Philippines as part of its research agenda.

Nevertheless, the HTA Council still noted the results of the unpublished laboratory and field experiments on Calcium hydroxide + Clinoptilolite *(Kiti-KitiX)* received from the proponent as shown in Annex B.

Another limitation of the review process is the restricted access to the Philippine FDA's evaluation report due to confidentiality concerns. The HTA Council was not able to review the evaluation report that the Philippine FDA used to approve the product, which could supplement this assessment.

7.4. Conclusion

Generally, there is limited evidence in the clinical efficacy/effectiveness and safety of Calcium hydroxide + Clinoptilolite larvicide *(Kiti-KitiX)* vs. previously utilized larvicides by the DOH and enhanced '4S' strategy in reducing dengue cases, severe cases and death due to dengue. There is a need for further studies to be conducted in order to provide the needed evidence that is responsive to its decision criteria based on the UHC Law.

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National Poison Management and Control Center, University of the Philippines (UP NPMCC)

Philippine Food and Drug Administration (FDA) - Cosmetics and Household/Urban Hazardous Substances Regulation and Research (CCHUHSRR)

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Annex A. List of studies from the systematic search that underwent title and abstract screening

	Author, year	Title	Reason for exclusion
Search Term: *(calcium hydroxide AND clinoptilolite) OR Kiti-kitiX*			
1	Czapik, P. (2023)	The Impact of Ions Contained in Concrete Pore Solutions on Natural Zeolites	Wrong PICO and study design; Not a clinical study
2	Wang YF, Lin F, Pang WQ (2007)	Ammonium exchange in aqueous solution using Chinese natural clinoptilolite and modified zeolite	Wrong PICO and study design; Not a clinical study
Search term: *(calcium hydroxide AND dengue) OR (calcium hydroxide AND larvae) OR (calcium hydroxide AND mosquito) OR (calcium hydroxide AND vector) OR (calcium hydroxide AND aedes)*			
3	Ataei F, Ahmadi A, Fasihi-R M, Kachoei R, Amani J, Najafi A. (2023)	Immunogenicity of different nanoparticle adjuvants containing recombinant RBD coronavirus antigen in animal model	Wrong PICO and study design.
4	Luo L, Jia W, Zhang Y, Guo Y, Zhu J, Li C. (2023)	Proprotein Convertase Furin Regulates Melanogenesis via the Notch Signaling Pathway	Wrong PICO and study design; Not a clinical study
5	Ali L, Sivaramakrishnan K, Kuttiyathil MS, Chandrasekaran V, Ahmed OH, Al-Harahsheh M, Altarawneh M (2023)	Prediction of Thermogravimetric Data in Bromine Captured from Brominated Flame Retardants (BFRs) in e-Waste Treatment Using Machine Learning Approaches	Wrong PICO and study design; Not a clinical study
6	Ortega E, Estrada LG, Bejarano EE, Cadena H. (2022)	Pintomyia evansi (Diptera: Psychodidae) larvae susceptibility to hydrated lime under laboratory conditions	Wrong PICO and study design; Not a clinical study
7	Gagnon P, Leskovec M, Prebil SD, Žigon R, Štokelj M, Raspor A, Peljhan S, Štrancar A. (2021)	Removal of empty capsids from adeno-associated virus preparations by multimodal metal affinity chromatography	Wrong PICO and study design; Not a clinical study
8	Schneeberg K, Bauernfeind R, Pohl H. (2017)	Comparison of cleaning methods for delicate insect specimens for scanning electron microscopy	Wrong PICO and study design; Not a clinical study
9	Zhang L, Qiu S, Huang T, Huang Z, Xu L, Wu C, Gelbic I, Guan X. (2013)	Effect of chemical additives on Bacillus thuringiensis (Bacillales: Bacillaceae) against Plutella xylostella (Lepidoptera: Pyralidae)	Wrong PICO and study design; Not a clinical study
10	Moingeon P. (2012)	Adjuvants for allergy vaccines	Wrong PICO and study design.
11	Estrada-Aguilar A, Sánchez-Manzano RM, Martínez-Ibarra JA, Camacho AD, Márquez-Navarro A, Nogueda-Torres B. (2012)	Larvicidal activity of micronized aqueous suspension of calcium hydroxide against *Aedes aegypti* and Culex quinquefasciatus (Diptera: Culicidae)	Wrong PICO and study design; Not a clinical study
12	Moingeon P, Lombardi V, Saint-Lu N, Tourdot S, Bodo V, Mascarell L. (2011)	Adjuvants and vector systems for allergy vaccines	Wrong PICO and study design.
13	Anderson MJ. (1966)	A Chemical Cue Induces Settlement of Sydney Rock Oysters, Saccostrea commercialis, in the Laboratory and in the Field	Wrong PICO and study design; Not a clinical study
14	Peterson RH, Martin-Robichaud DJ, Power J. (1988)	Toxicity of potash brines to early developmental stages of Atlantic salmon (Salmo salar)	Wrong PICO and study design.

	Author, year	Title	Reason for exclusion
15	Xavier PA, Braun RF, Pinheiro Pda S, Monteiro WJ, Araujo N, do Nascimento SR. (1982)	[Effect of calcium hydroxide as a molluscacide]	Wrong PICO and study design.
Search Term: *(clinoptilolite AND dengue) OR (clinoptilolite AND larvae) OR (clinoptilolite AND mosquito) OR (clinoptilolite AND vector) OR (clinoptilolite AND aedes)*			
16	da Silva CP, Seremeta DCH, Pedroso CR, Folle NMT, Souza ATDC, Barreto LS, de Oliveira EC, de Oliveira Ribeiro CA, Vidal CMS, de Campos SX. (2020)	Effects of different filtration techniques on quality and toxicology of post treatment effluent from an anaerobic reactor	Wrong PICO and study design.
17	Langellotti CA, Pappalardo JS, Quattrocchi V, Mongini C, Zamorano P. (2011)	Induction of specific cytotoxic activity for bovine herpesvirus-1 by DNA immunization with different adjuvants	Wrong PICO and study design; Not a clinical study
Search Term: *(calcium hydroxide OR clinoptilolite)*			
18	Agdamag ASC, Aggabao LHC, Agudo MSC, Alcachupas FLM, Alejo JCV, Altamera SA, Antonio JND, Arbizo JL, Arroyo JJH, Bañez DRD, Balaong VBB, Belo NAR, Bernardo NL, Besa JJV, Beza JHM, Dela Rosa TL (2020)	Anti-urolithiatic Activity of Sambong (Blumea balsamifera) Extract in Ethylene Glycol-induced Urolithiatic Wistar Rats (Rattus norvegicus)	Wrong Population, Intervention
19	Torres-Ticzon V-MF, Alesna-Llanto E, Nancho RMH (2020)	The Nutritional Status of Filipino Pregnant Adolescents 14 to 19 Years Old in a Tertiary Hospital	Wrong Population, Intervention
20	Simon KJD, Elopre WJO (2020)	Nutritional Evaluation of Therapeutic Diets for Cardiovascular Diseases in Hospitals of General Santos City, Philippines: A Comparative Cross-sectional Study	Wrong Population, Intervention
21	Janica McKaye L. Berboso , Kristine May P. Gomez , Nino Christopher T. Misplacido , Banley J. Roque	A Thesis Presented to the Faculty of the College of Medical Technology Manila Central University.	Wrong PICO and study design
22	Grace F. Barrera	Comparative Study Between the Effects of Calcium Hydroxide and Zinc Oxide Eugenol in RCT.	Wrong PICO and study design
23	Vicente C. Mallari Jr. , Orlando R. Pulido , Rico J. Cabangon , Loreto A. Novicio	Development of Rapid Curing Process for Cement-Bonded Board Manufacture.	Wrong PICO and study design
24	VO . Medina III, K . Shinkai , M . Shirono , N . Tanaka , Y . Katoh	Histopathologic study on pulp response to single-bottle and self-etching adhesive systems.	Wrong PICO and study design
25	Janica . McKaye , Kristine May . Gomez , Nino Christoper . Misplacido , Banley . Roque , Josephine . Abrazaldo	The potential anticoagulant effect of humic substances from soil fertilizer.	Wrong PICO and study design
26	Rene B. Blancaver	Primary renal magnesium wasting with hypercalciuria in a 39-year-old female: A case report.	Wrong PICO and study design
27	Borromeo JDP	A review on calcium hydroxide as an intracanal medicament in root canal therapy.	Wrong PICO and study design
28	Chan JCM	New treatment modalities for pediatric kidney disease.	Wrong PICO and study design
29	Jose Daniel P. Borromeo	A review on calcium hydroxide as an intracanal medicament in root canal therapy.	Wrong PICO and study design

	Author, year	Title	Reason for exclusion
30	Mary Ann A. Javate , Irish O. Kho , Mirasol G. Lacbayo , Junna E. Macalisang , Bahareh . Rashnavady , Terng . Wen Lue , Karen A. Yu , Leonila D. Tan	The effect of calcium hydroxide and camphorated monochlorophenol intracanal medicament on the bacterial count of maxillary anterior teeth undergoing root canal treatment among the patients of Cebu Doctors' College Dental Infirmary	Wrong PICO and study design
Search term: *(calcium hydroxide OR clinoptilolite) AND (safety)*			
31	Smaïl-Faugeron V, Glenny AM, Courson F, Durieux P, Muller-Bolla M, Fron Chabouis H.	Pulp treatment for extensive decay in primary teeth	wrong PICO and study design
32	Aliabadi T, Saberi EA, Motameni Tabatabaei A, Tahmasebi E.	Antibiotic use in endodontic treatment during pregnancy: A narrative review	wrong PICO and study design
33	Kang SJ, Cho YS, Lee TH, Kim SE, Ryu HS, Kim JW, Park SY, Lee YJ, Shin JE; Constipation Research Group of the Korean Society of Neurogastroenterology and Motility.	Medical Management of Constipation in Elderly Patients: Systematic Review	wrong PICO and study design
34	Brizuela C, Meza G, Urrejola D, Quezada MA, Concha G, Ramírez V, Angelopoulos I, Cadiz MI, Tapia-Limonchi R, Khoury M.	Cell-Based Regenerative Endodontics for Treatment of Periapical Lesions: A Randomized, Controlled Phase I/II Clinical Trial	wrong PICO and study design
35	Kraljević Pavelić S, Simović Medica J, Gumbarević D, Filošević A, Pržulj N, Pavelić K.	Critical Review on Zeolite Clinoptilolite Safety and Medical Applications in vivo	Wrong intervention
36	Wells C, Dulong C, McCormack S.	Vital Pulp Therapy for Endodontic Treatment of Mature Teeth: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines	wrong PICO and study design
37	Anderle K, Wolzt M, Moser G, Keip B, Peter J, Meisslitzer C, Gouya G, Freissmuth M, Tschegg C.	Safety and efficacy of purified clinoptilolite-tuff treatment in patients with irritable bowel syndrome with diarrhea: Randomized controlled trial	Wrong intervention
38	Benzoni T, Hatcher JD.	Bleach Toxicity	wrong PICO and study design
39	Laky M, Volmer M, Arslan M, Agis H, Moritz A, Cvikl B.	Efficacy and Safety of Photon Induced Photoacoustic Streaming for Removal of Calcium Hydroxide in Endodontic Treatment	wrong PICO and study design
40	Zhang Y, Gao W, Ni W, Zhang S, Li Y, Wang K, Huang X, Fu P, Hu W.	Influence of calcium hydroxide addition on arsenic leaching and solidification/stabilisation behaviour of metallurgical-slag-based green mining fill	wrong PICO and study design
41	Nizet S, Muñoz E, Fiebich BL, Abuja PM, Kashofer K, Zatloukal K, Tangermann S, Kenner L, Tschegg C, Nagl D, Scheichl L, Meisslitzer-Ruppitsch C, Freissmuth M, Berger T.	Clinoptilolite in Dextran Sulphate Sodium-Induced Murine Colitis: Efficacy and Safety of a Microparticulate Preparation	wrong PICO and study design
42	Chandwani ND, Maurya N, Nikhade P, Chandwani J.	Comparative evaluation of antimicrobial efficacy of calcium hydroxide, triple antibiotic paste and bromelain against Enterococcus faecalis: An In Vitro study	wrong PICO and study design

	Author, year	Title	Reason for exclusion
43	Feldman JM, Hendrickx J, Kennedy RR.	Carbon Dioxide Absorption During Inhalation Anesthesia: A Modern Practice	wrong PICO and study design
44	Cernaro V, Longhitano E, Calabrese V, Casuscelli C, Di Carlo S, Spinella C, Gembillo G, Santoro D.	Progress in pharmacotherapy for the treatment of hyperphosphatemia in renal failure	wrong PICO and study design
45	Almeida GM, Carvalho VHM, Silva ÉBP, Cançado MAF, Barroso LS, Queiroz EL, An TL, Ribeiro APD, Carvalho-Junior JR, Leite AF.	Periradicular repair after single- and two-visit root canal treatments using ultrasonic irrigant activation and calcium hydroxide dressing of teeth with apical periodontitis: study protocol for randomized controlled trials	wrong PICO and study design
46	Malberti F, Surian M, Poggio F, Minoia C, Salvadeo A.	Efficacy and safety of long-term treatment with calcium carbonate as a phosphate binder	wrong PICO and study design
47	Hugar SM, Kukreja P, Hugar SS, Gokhale N, Assudani H.	Comparative Evaluation of Clinical and Radiographic Success of Formocresol, Propolis, Turmeric Gel, and Calcium Hydroxide on Pulpotomized Primary Molars: A Preliminary Study	wrong PICO and study design
48	Wang Y, Luo S, Tang W, Yang L, Liao Y, Liu F.	Efficacy and safety of mineral trioxide aggregate (MTA) pulpotomy for caries-exposed permanent teeth in children: a systematic review and meta-analysis	wrong PICO and study design
49	Elmore AR; Cosmetic Ingredient Review Expert Panel.	Final report on the safety assessment of aluminum silicate, calcium silicate, magnesium aluminum silicate, magnesium silicate, magnesium trisilicate, sodium magnesium silicate, zirconium silicate, attapulgite, bentonite, Fuller's earth, hectorite, kaolin, lithium magnesium silicate, lithium magnesium sodium silicate, montmorillonite, pyrophyllite, and zeolite	wrong PICO and study design
50	Zhao J, Zhang Y, Xue D, Cui C, Li W, Liu F.	Nanoscale Insights into the Mechanical Behavior of Interfacial Composite Structures between Calcium Silicate Hydrate/Calcium Hydroxide and Silica	wrong PICO and study design
51	Kazama JJ.	Oral phosphate binders: history and prospects	wrong PICO and study design
52	Guo J, Zhang N, Cheng Y.	Comparative efficacy of medicaments or techniques for pulpotomy of primary molars: a network meta-analysis	wrong PICO and study design
53	Compalati E, Incorvaia C, Cavaliere C, Masieri S, Gargiulo A, Mistrello G, Frati F.	The role of allergoids in allergen immunotherapy: from injective to sublingual route	wrong PICO and study design
54	Johanson JF.	Review of the treatment options for chronic constipation	wrong PICO and study design
55	Saha S, Nair R, Asrani H.	Comparative Evaluation of Propolis, Metronidazole with Chlorhexidine, Calcium Hydroxide and Curcuma Longa Extract as Intracanal Medicament Against E.faecalis- An Invitro Study	wrong PICO and study design
56	Romanazzi G, Orçonneau Y, Moumni M, Davillerd Y, Marchand PA.	Basic Substances, a Sustainable Tool to Complement and Eventually Replace Synthetic Pesticides in the Management of Pre and Postharvest Diseases: Reviewed Instructions for Users	wrong PICO and study design

	Author, year	Title	Reason for exclusion
57	Goto N, Kato H, Maeyama J, Shibano M, Saito T, Yamaguchi J, Yoshihara S.	Local tissue irritating effects and adjuvant activities of calcium phosphate and aluminium hydroxide with different physical properties	wrong PICO and study design
58	Kopel HM.	The pulp capping procedure in primary teeth "revisited"	wrong PICO and study design
59	Ngamsurach P, Nemkhuntod S, Chanaphan P, Praipipat P.	Modified Beaded Materials from Recycled Wastes of Bagasse and Bagasse Fly Ash with Iron(III) Oxide-Hydroxide and Zinc Oxide for the Removal of Reactive Blue 4 Dye in Aqueous Solution	wrong PICO and study design
60	Więckol-Ryk A, Thomas M, Białecka B.	Solid Peroxy Compounds as Additives to Organic Waste for Reclamation of Post-Industrial Contaminated Soils	wrong PICO and study design
61	Poosapati A, Ambade RB, Madan D.	Flexible and Safe Additives-Based Zinc-Binder-Free-Hierarchical MnO(2) -Solid Alkaline Polymer Battery for Potential Wearable Applications	wrong PICO and study design
62	Kraljević Pavelić S, Saftić Martinović L, Simović Medica J, Žuvić M, Perdija Ž, Krpan D, Eisenwagen S, Orct T, Pavelić K.	Clinical Evaluation of a Defined Zeolite-Clinoptilolite Supplementation Effect on the Selected Blood Parameters of Patients	Wrong intervention
63	Lewis B.	The obsolescence of formocresol	wrong PICO and study design
64	Odukoya JO, De Saeger S, De Boevre M, Adegoke GO, Audenaert K, Croubels S, Antonissen G, Vermeulen K, Gbashi S, Njobeh PB.	Effect of Selected Cooking Ingredients for Nixtamalization on the Reduction of Fusarium Mycotoxins in Maize and Sorghum	wrong PICO and study design
65	Praipipat P, Ngamsurach P, Prasongdee V.	Comparative Reactive Blue 4 Dye Removal by Lemon Peel Bead Doping with Iron(III) Oxide-Hydroxide and Zinc Oxide	wrong PICO and study design
66	Sato E, Ochi Y, Horiguchi H, Takenaka K, Wu J, Parthasarathy R, Komoda Y, Ohmura N.	Effect of Baffle Clearance on Scale Deposition in an Agitated Vessel	wrong PICO and study design
67	Sishi VNB, Van Wyk JC, Khumalo NP.	The pH of lye and no-lye hair relaxers, including those advertised for children, is at levels that are corrosive to the skin	wrong PICO and study design
68	Ren SZ, Zhu XH, Wang B, Liu M, Li SK, Yang YS, An H, Zhu HL.	A versatile nanoplatform based on multivariate porphyrinic metal-organic frameworks for catalytic cascade-enhanced photodynamic therapy	wrong PICO and study design
69	Krishna R, East L, Larson P, Valiathan C, Butterfield K, Teng Y, Hernandez-Illas M.	Effect of metal-cation antacids on the pharmacokinetics of 1200 mg raltegravir	wrong PICO and study design
70	Liu Q, Zhuang Y, Shi B.	Three-dimensional reduced graphene reinforced cement with enhanced safety and durability for drinking water distribution applications: Long-term experimental and theoretical study	wrong PICO and study design
71	Dolanc I, Ferhatović Hamzić L, Orct T, Micek V, Šunić I, Jonjić A, Jurasović J, Missoni S, Čoklo M, Pavelić SK.	The Impact of Long-Term Clinoptilolite Administration on the Concentration Profile of Metals in Rodent Organisms	Wrong population and study design
72	Li Y, Zhang H, Huang G, Cui Y, Feng J, Zhang Y, Li D,	Preparation and Properties of Municipal Solid Waste Incineration Alkali-Activated	wrong PICO and study design

	Author, year	Title	Reason for exclusion
	Zhu J.	Lightweight Materials through Spontaneous Bubbles	
73	Goto N, Kato H, Maeyama J, Eto K, Yoshihara S.	Studies on the toxicities of aluminium hydroxide and calcium phosphate as immunological adjuvants for vaccines	wrong PICO and study design
74	Gianni S, Morais CCA, Larson G, Pinciroli R, Carroll R, Yu B, Zapol WM, Berra L.	Ideation and assessment of a nitric oxide delivery system for spontaneously breathing subjects	wrong PICO and study design
75	Jensen-Jarolim E, Roth-Walter F, Jordakieva G, Pali-Schöll I.	Allergens and Adjuvants in Allergen Immunotherapy for Immune Activation, Tolerance, and Resilience	wrong PICO and study design
76	Zhou S, Du Y, Feng Y, Sun H, Xia W, Yuan H.	Stabilization of arsenic and antimony Co-contaminated soil with an iron-based stabilizer: Assessment of strength, leaching and hydraulic properties and immobilization mechanisms	wrong PICO and study design
77	Gong T, Wang Z, Zhang Y, Zhang Y, Hou M, Liu X, Wang Y, Zhao L, Ruse ND, Troczynski T, Häfeli UO.	A Comprehensive Study of Osteogenic Calcium Phosphate Silicate Cement: Material Characterization and In Vitro/In Vivo Testing	wrong PICO and study design
78	Salusky IB, Foley J, Nelson P, Goodman WG.	Aluminum accumulation during treatment with aluminum hydroxide and dialysis in children and young adults with chronic renal disease	wrong PICO and study design
79	Mounir MMF, Farsi JMA, Alhazzazi TY, Matar MA, El-Housseiny AA.	Characterization of the apical bridge barrier formed following amelogenin apexification	wrong PICO and study design
80	Dahake PT, Thosar N, Hande A, Joshi DA, Bhagat A.	Hematological and Biochemical Responses of Newly Formulated Primary Root Canal Obturating Material: An In Vivo Study	wrong PICO and study design
81		Erratum to Clinoptilolite in Dextran Sulphate Sodium-Induced Murine Colitis: Efficacy and Safety of a Microparticulate Preparation	Wrong study design, wrong population
82	Alauddin MS, Mohammad N, Jaafar A, Abdul Fatah F, Ahmad AA.	A Contemporary Evaluation on Posterior Direct Restoration Teaching among Undergraduates in Dental Schools in Malaysia	Wrong study design, wrong population
83	Nilsen BW, Jensen E, Örtengren U, Michelsen VB.	Analysis of organic components in resin-modified pulp capping materials: critical considerations	Wrong study design
84	Hossain MF, Islam MS, Kashem MA, Osman KT, Zhou Y.	Lead immobilization in soil using new hydroxyapatite-like compounds derived from oyster shell and its uptake by plant	Wrong study design
85	Chen XB, Li C, Xu D.	Biodegradation of Mg-14Li alloy in simulated body fluid: A proof-of-concept study	Wrong study design
86	Jung CA, Torgerson PP, Bolt R, Grimm F, Schädler J, Albini S, Liesegang A.	Alternatives to robenidine to control gastrointestinal disorders of weaner rabbits in the field	Wrong study design, wrong population
87	Waterhouse PJ.	Formocresol and alternative primary molar pulpotomy medicaments: a review	Wrong study design
88	Restrepo Valencia CA, Cruz J.	[Safety and effectiveness of nicotinic acid in the management of patients with chronic renal disease and hyperlipidemia associated to hyperphosphatemia]	Wrong intervention, wrong population
89	Słota ET, Vasylechko VO, Yaremko ZM, Bagday SR, Poddubnaya O, Puziy AM.	Neodymium sorption on the Na-form of Transcarpathian clinoptilolite	Wrong study design

	Author, year	Title	Reason for exclusion
90	Kato H, Shibano M, Saito T, Yamaguchi J, Yoshihara S, Goto N.	Relationship between hemolytic activity and adsorption capacity of aluminum hydroxide and calcium phosphate as immunological adjuvants for biologicals	Wrong study design
91	Zhai Y, Pérez-Díaz IM.	Fermentation Cover Brine Reformulation for Cucumber Processing with Low Salt to Reduce Bloater Defect	Wrong study design
92	Deinsberger J, Marquart E, Nizet S, Meisslitzer C, Tschegg C, Uspenska K, Gouya G, Niederdöckl J, Freissmuth M, Wolzt M, Weber B.	Topically administered purified clinoptilolite-tuff for the treatment of cutaneous wounds: A prospective, randomised phase I clinical trial	Wrong intervention
93	Li Z, Wu L, Sun S, Gao J, Zhang H, Zhang Z, Wang Z.	Disinfection and removal performance for Escherichia coli, toxic heavy metals and arsenic by wood vinegar-modified zeolite	Wrong study design
94	Lee JI, Kang JK, Hong SH, Lee CG, Jeong S, Park SJ.	Thermally treated Mytilus coruscus shells for fluoride removal and their adsorption mechanism	Wrong study design
95	Yang H, Kang JK, Park SJ, Lee CG.	Phosphorus recovery from cattle manure bottom ash by extraction and precipitation methods	Wrong study design
96	Chen G, Yao N, Ye Y, Fu F, Hu N, Zhang Z.	Study on mechanical properties and damage characteristics of cemented waste rock-tailing backfill	Wrong study design
97	Sun G, Tang Q, Zhang J, Liu Z.	Early activation of high volume fly ash by ternary activator and its activation mechanism	Wrong study design
98	Adamis Z, Tátrai E, Honma K, Six E, Ungváry G.	In vitro and in vivo tests for determination of the pathogenicity of quartz, diatomaceous earth, mordenite and clinoptilolite	Wrong study design, wrong population
99	Kim ES, Md S, Seo SG, Kang IW, Yoon HS.	Reduction of Fluoride in Water Phase by Micro-Nano Bubble Pretreatment Process	Wrong study design
100	Wang Q, Ma Y, Wang F, Shi Z, You H, Tian Y, Liu Y, Hu Z, Song H, Wang D, Sun Y, Yang R, Sun H.	Experimental Study on Carbonation Durability of Kaolin Strengthened with Slag Portland Cement	Wrong study design
101	Martins MR, Carvalho MF, Pina-Vaz I, Capelas JA, Martins MA, Gutknecht N.	Outcome of Er,Cr:YSGG laser-assisted treatment of teeth with apical periodontitis: a blind randomized clinical trial	Wrong study design, wrong population
102	Spengler K, Follmann H, Boos KS, Seidel D, von der Haar F, Elsner R, Maywald F.	Cross-linked iron dextran is an efficient oral phosphate binder in the rat	Wrong study design, wrong population
103	Zhao T, Doyle MP.	Reduction of Campylobacter jejuni on chicken wings by chemical treatments	Wrong study design, wrong population
104	Feng Y, Zhang Q, Chen Q, Wang D, Guo H, Liu L, Yang Q.	Hydration and strength development in blended cement with ultrafine granulated copper slag	Wrong study design
105	Williams DD, Peng B, Bailey CK, Wire MB, Deng Y, Park JW, Collins DA, Kapsi SG, Jenkins JM.	Effects of food and antacids on the pharmacokinetics of eltrombopag in healthy adult subjects: two single-dose, open-label, randomized-sequence, crossover studies	Wrong study design, wrong population
106	Lu N, Ran X, Pan Z, Korayem AH.	Use of Municipal Solid Waste Incineration Fly Ash in Geopolymer Masonry Mortar	Wrong study design

	Author, year	Title	Reason for exclusion
		Manufacturing	
107	Arroyo D, Panizo N, Abad S, Vega A, Pérez-de José A, López-Gómez JM.	The effect of replacing aluminium hydroxide with calcium acetate/magnesium carbonate on serum phosphorus control in haemodialysis patients	Wrong intervention wrong population
108	Weinreich T, Passlick-Deetjen J, Ritz E.	Low dialysate calcium in continuous ambulatory peritoneal dialysis: a randomized controlled multicenter trial. The Peritoneal Dialysis Multicenter Study Group	Wrong intervention, wrong population
109	Wu CC, Roan RT, Chen JH.	Sintering mechanism of the CaF2 on hydroxyapatite by a 10.6-l microm CO2 laser	Wrong study design
110	Zhao Y, Chen M, Zhang Q, Yuan W, Wu Y.	Ion exchange to immobilize Cd(II) at neutral pH into silicate matrix prepared by co-grinding kaolinite with calcium compounds	Wrong study design
111	Mayura K, Abdel-Wahhab MA, McKenzie KS, Sarr AB, Edwards JF, Naguib K, Phillips TD.	Prevention of maternal and developmental toxicity in rats via dietary inclusion of common aflatoxin sorbents: potential for hidden risks	Wrong study design, wrong population
112	Kielė A, Vaičiukynienė D, Tamošaitis G, Bistrickaitė R.	Thermal Properties of Alkali Activated Slag Plaster for Wooden Structures	Wrong study design
113	Jung H, Shin T, Cho N, Kim TK, Kim J, Ryu TI, Song KB, Hwang SR, Ryu BH, Han B.	Thermochemical study for remediation of highly concentrated acid spill: Computational modeling and experimental validation	Wrong study design
114	Kharasch ED, Powers KM, Artru AA.	Comparison of Amsorb, sodalime, and Baralyme degradation of volatile anesthetics and formation of carbon monoxide and compound a in swine in vivo	Wrong study design
115	Pap S, Kirk C, Bremner B, Turk Sekulic M, Gibb SW, Maletic S, Taggart MA.	Synthesis optimisation and characterisation of chitosan-calcite adsorbent from fishery-food waste for phosphorus removal	Wrong study design
116	Oriowo OM, Chou BR, Cullen AP.	Glassblowers' ocular health and safety: optical radiation hazards and eye protection assessment	Wrong study design
117	Jalili M, Jinap S.	Reduction of mycotoxins in white pepper	Wrong study design
118	Pan Z, Hu S, Zhang C, Zhou T, Hua G, Li Y, Lv X.	Mechanical and Hydration Characteristics of Stabilized Gold Mine Tailings Using a Sustainable Industrial Waste-Based Binder	Wrong study design
119	Song Y, Guo Z, Wang R, Yang L, Cao Y, Wang H.	A novel approach for treating acid mine drainage by forming schwertmannite driven by a combination of biooxidation and electroreduction before lime neutralization	Wrong study design
120	Lee SH, Lee SG, Lee JS, Ma BC.	Understanding the Flame Retardant Mechanism of Intumescent Flame Retardant on Improving the Fire Safety of Rigid Polyurethane Foam	Wrong study design
121	Cheng H, Song Y, Bian Y, Ji R, Wang F, Gu C, Yang X, Ye M, Ouyang G, Jiang X.	Meso-/microporous carbon as an adsorbent for enhanced performance in solid-phase microextraction of chlorobenzenes	Wrong study design
122	Snell P, Oo C, Dorr A, Barrett J.	Lack of pharmacokinetic interaction between the oral anti-influenza neuraminidase inhibitor prodrug oseltamivir and antacids	Wrong study design
123	Li Y, Yao N, Ye Y, Wu M, Chen G, Tan B, Guan W.	Mechanical properties and damage constitutive model of phosphogypsum-based cemented backfill under hydrochemical action	Wrong study design
124	Robijn S, Vervaet BA, D'Haese PC, Verhulst A.	Evaluation of intestinal phosphate binding to improve the safety profile of oral	Wrong study design, wrong

	Author, year	Title	Reason for exclusion
		sodium phosphate bowel cleansing	population
125	Barbosa JC, Correia DM, Fidalgo-Marijuan A, Gonçalves R, Ferdov S, de Zea Bermudez V, Lanceros-Mendez S, Costa CM.	High Performance Ternary Solid Polymer Electrolytes Based on High Dielectric Poly(vinylidene fluoride) Copolymers for Solid State Lithium-Ion Batteries	Wrong study design
126	Moriniere P, Hocine C, Boudailliez B, Belbrik S, Renaud H, Westeel PF, Solal MC, Fournier A.	Long-term efficacy and safety of oral calcium as compared to A1(OH)3 as phosphate binders	Wrong study design
127	Sun L, Duan S, Zhang S, Cheng W, Wang G, Cao X.	Influencing factors and mechanism of CO(2) adsorption capacity of FA-based carbon sequestration materials	Wrong study design
128	Sturtevant JM, Hawley CM, Reiger K, Johnson DW, Campbell SB, Burke JR, Bofinger A, Isbel NM.	Efficacy and side-effect profile of sevelamer hydrochloride used in combination with conventional phosphate binders	Wrong study design
129	Kim NH, Lee NY, Kim SH, Lee HJ, Kim Y, Ryu JH, Rhee MS.	Optimization of low-temperature blanching combined with calcium treatment to inactivate Escherichia coli O157:H7 on fresh-cut spinach	Wrong study design
130	Spotti M, Fracchiolla ML, Arioli F, Caloni F, Pompa G.	Aflatoxin B1 binding to sorbents in bovine ruminal fluid	Wrong study design
131	Barbosa JC, Correia DM, Fernández EM, Fidalgo-Marijuan A, Barandika G, Gonçalves R, Ferdov S, de Zea Bermudez V, Costa CM, Lanceros-Mendez S.	High-Performance Room Temperature Lithium-Ion Battery Solid Polymer Electrolytes Based on Poly(vinylidene fluoride-co-hexafluoropropylene) Combining Ionic Liquid and Zeolite	Wrong study design
132	Yu B, Ferrari M, Schleifer G, Blaesi AH, Wepler M, Zapol WM, Bloch DB.	Development of a portable mini-generator to safely produce nitric oxide for the treatment of infants with pulmonary hypertension	Wrong population, intervention
133	Tabibian M, Torbati M, Afshar Mogaddam MR, Mirlohi M, Sadeghi M, Mohtadinia J.	Evaluation of Vitamin D(3) and D(2) Stability in Fortified Flat Bread Samples During Dough Fermentation, Baking and Storage	Wrong study design
134	Nishimura H, Higo Y, Ohno M, Tsutsui TW, Tsutsui T.	Ability of root canal antiseptics used in dental practice to induce chromosome aberrations in human dental pulp cells	Wrong study design
135	Barbosa JC, Correia DM, Fidalgo-Marijuan A, Gonçalves R, Ferdov S, de Zea Bermudez V, Costa CM, Lanceros-Mendez S.	Influence of Solvent Evaporation Temperature on the Performance of Ternary Solid Polymer Electrolytes Based on Poly(vinylidene fluoride-co-hexafluoropropylene) Combining an Ionic Liquid and a Zeolite	Wrong study design
136	Westfelt UN, Lundin S, Stenqvist O.	Safety aspects of delivery and monitoring of nitric oxide during mechanical ventilation	Wrong study design
137	Jalili M, Jinap S, Son R.	The effect of chemical treatment on reduction of aflatoxins and ochratoxin A in black and white pepper during washing	Wrong study design
138	Jahanbakhsh S, Kabore KP, Fravalo P, Letellier A,	Impact of medicated feed along with clay mineral supplementation on Escherichia	Wrong study design

	Author, year	Title	Reason for exclusion
	Fairbrother JM.	coli resistance to antimicrobial agents in pigs after weaning in field conditions	
139	Mao L, Wang J, Zeng M, Zhang W, Hu L, Peng M.	Temperature dependent reduction of Cr(VI) to Cr(V) aroused by CaO during thermal treatment of solid waste containing Cr(VI)	Wrong study design
140	Alvarado-Casillas S, Ibarra-Sánchez S, Rodríguez-García O, Martínez-Gonzáles N, Castillo A.	Comparison of rinsing and sanitizing procedures for reducing bacterial pathogens on fresh cantaloupes and bell peppers	Wrong study design
141	Jahanbakhsh S, Letellier A, Fairbrother JM.	Circulating of CMY-2 β-lactamase gene in weaned pigs and their environment in a commercial farm and the effect of feed supplementation with a clay mineral	Wrong study design
142	Chen Q, Sun S, Wang Y, Zhang Q, Zhu L, Liu Y.	In-situ remediation of phosphogypsum in a cement-free pathway: Utilization of ground granulated blast furnace slag and NaOH pretreatment	Wrong study design
143	Harvey D, Pollock NW, Gant N, Hart J, Mesley P, Mitchell SJ.	The duration of two carbon dioxide absorbents in a closed-circuit rebreather diving system	Wrong study design
144	Wang D, Ma ZH, Pan LG, Han P, Zhao L, Wang JH.	[Research on the quantitative determination of lime in wheat flour by near-infrared spectroscopy]	Wrong study design
145	Mofenson HC, Caraccio TR.	Magnesium intoxication in a neonate from oral magnesium hydroxide laxative	Wrong population, intervention
146	Scouten AJ, Beuchat LR.	Combined effects of chemical, heat and ultrasound treatments to kill Salmonella and Escherichia coli O157:H7 on alfalfa seeds	Wrong study design
147	Garaj-Vrhovac V, Oreščanin V, Gajski G, Gerić M, Ruk D, Kollar R, Radić Brkanac S, Cvjetko P.	Toxicological characterization of the landfill leachate prior/after chemical and electrochemical treatment: a study on human and plant cells	Wrong study design
148	Shalapy A, Zhao S, Zhang C, Li Y, Geng H, Ullah S, Wang G, Huang S, Liu Y.	Adsorption of Deoxynivalenol (DON) from Corn Steep Liquor (CSL) by the Microsphere Adsorbent SA/CMC Loaded with Calcium	Wrong study design
149	Riem N, Boet S, Chandra D.	Setting standards for simulation in anesthesia: the role of safety criteria in accreditation standards	Wrong study design
150	Bell GT.	Problems with soda lime	Wrong study design
151	Marini F, Bellugi I, Gambi D, Pacenti M, Dugheri S, Focardi L, Tulli G.	Compound A, formaldehyde and methanol concentrations during low-flow sevoflurane anaesthesia: comparison of three carbon dioxide absorbers	Wrong study design
152	Han DH, Lee JH.	Effects of liming on uptake of lead and cadmium by Raphanus sativa	Wrong study design
153	Beuchat LR, Scouten AJ.	Combined effects of water activity, temperature and chemical treatments on the survival of Salmonella and Escherichia coli O157:H7 on alfalfa seeds	Wrong study design
154	Burnett CA, Lushniak BD, McCarthy W, Kaufman J.	Occupational dermatitis causing days away from work in U.S. private industry, 1993	Wrong study design
155	Jemmali M.	Decontamination and detoxification of mycotoxins	Wrong study design
156	Ahmadsah LS, Min SG, Han SK, Hong Y, Kim HY.	Effect of Low Salt Concentrations on Microbial Changes During Kimchi	Wrong study design

	Author, year	Title	Reason for exclusion
		Fermentation Monitored by PCR-DGGE and Their Sensory Acceptance	
157	Liley A.	Problems with soda lime	Wrong study design
158	Chartier D, Muzeau B, Stefan L, Sanchez-Canet J, Monguillon C.	Magnesium alloys and graphite wastes encapsulated in cementitious materials: Reduction of galvanic corrosion using alkali hydroxide activated blast furnace slag	Wrong study design
159	Baum J, Sachs G, vd Driesch C, Stanke HG.	Carbon monoxide generation in carbon dioxide absorbents	Wrong study design
160	Krajišnik D, Stepanović-Petrović R, Tomić M, Micov A, Ibrić S, Milić J.	Application of artificial neural networks in prediction of diclofenac sodium release from drug-modified zeolites physical mixtures and antiedematous activity assessment	Wrong study design
161	Mihaly-Cozmuta L, Mihaly-Cozmuta A, Peter A, Nicula C, Tutu H, Silipas D, Indrea E.	Adsorption of heavy metal cations by Na-clinoptilolite: equilibrium and selectivity studies	Wrong study design
162	Fang ZX, Eger EI 2nd.	Factors affecting the concentration of compound A resulting from the degradation of sevoflurane by soda lime and Baralyme in a standard anesthetic circuit	Wrong study design
163	Rendell-Baker L.	Problems with anesthetic gas machines and their solutions	Wrong study design
164	Morgan DL.	NTP Toxicity Study Report on the atmospheric characterization, particle size, chemical composition, and workplace exposure assessment of cellulose insulation (CELLULOSEINS)	Wrong study design
165	Lee D.	Formation of leadhillite and calcium lead silicate hydrate (C-Pb-S-H) in the solidification/stabilization of lead contaminants	Wrong study design
166	Holliday SL, Scouten AJ, Beuchat LR.	Efficacy of chemical treatments in eliminating Salmonella and Escherichia coli O157:H7 on scarified and polished alfalfa seeds	Wrong study design
167	Grabow WO, Middendorff IG, Basson NC.	Role of lime treatment in the removal of bacteria, enteric viruses, and coliphages in a wastewater reclamation plant	Wrong study design
168	Lillo RS, Ruby A, Gummin DD, Porter WR, Caldwell JM.	Chemical safety of U.S. Navy Fleet soda lime	Wrong study design
169	Giddey C, Bunter G, Larroux R, Jemmali M, Rossi J.	Detoxification of aflatoxin-polluted peanut cakes with monomethylamine/Ca(OH)2: pilot industrial application, nutrition experiments, toxicity evaluation	Wrong study design
170	Kortmiš MV, Maltar-Strmečki N.	DOSE RECONSTRUCTION FROM ESR SIGNAL OF GAMMA-IRRADIATED SODA-LIME GLASS FOR TRIAGE APPLICATION	Wrong study design
171	Janshon GP, Dudziak R.	[Interactions of dry soda lime with enflurane and sevoflurane. Clinical report on two unusual anesthesias]	Wrong population, intervention
172	Vasylechko VO, Gryshchouk GV, Zakordonskiy VP, Vyviurska O, Pashuk AV.	A solid-phase extraction method using Transcarpathian clinoptilolite for preconcentration of trace amounts of terbium in water samples	Wrong study design
173	Myers CL, Stanley HR, Heyde JB, Chamberlain J.	Primate pulpal response to ultraviolet light-polymerized direct-bonding material systems	Wrong study design

	Author, year	Title	Reason for exclusion
174	Morimoto Y, Tamura T, Matsumoto S, Nakamura M, Makino A, Oka H, Shimizu K, Miyauchi Y.	[Carbon monoxide concentrations during low flow anesthesia]	Wrong study design
175	Schrieber R, Seybold U.	Gelatine production, the six steps to maximum safety	Wrong study design
176	Gaye F, Mbaye M, Diop-Thiaw F, Ndiaye D.	[Treatment of Baume class IV pulp diseases with calcium hydroxide: a clinical experimental study in Dakar]	Wrong study design
177	Taber TE, Hegemen TF, York S.	Calcium carbonate as a phosphate binder in hemodialysis patients	Wrong population, intervention
178	Ramarapu S, Ramakrishnan U.	An unusual cause of anesthesia circuit blockade by SODASORB PRE-PAK	Wrong study design
179	Detmer MD, Chandra P, Cohen PJ.	Occurrence of hypercarbia due to an unusual failure of anesthetic equipment	Wrong study design

Annex B: List of Studies Submitted by the Proponent

	Author, year	Title	Study Design	Population	Intervention	Comparator	Outcomes	Results	Reason for exclusion
Nomination Dossier									
1	Ferdinand V. Salazar MSC DAP&E PhD FPA Accredited Researcher, Exterminator, and Fumigator (2008-2009)	Evaluation of Larvicidal Activity of Calcium Hydroxide/Clinoptilolite against Dengue Vectors	Field Simulation Experiment	aedes aegypti larvae Laboratory experiment	Clinoptilolite at different concentrations	Insecticide (temephos)	Mortality of Aedes aegypti larvae	I: 100% larval mortality C: 100% larval mortality	Wrong PICO and study design.
2	Ferdinand V. Salazar MSC DAP&E PhD FPA Accredited Researcher, Exterminator, and Fumigator (2008-2009)	24 HR Laboratory Field Simulation of Calcium Hydroxide/ Clinoptilolite through Vector Control	Methodology not provided						
3	P.A. Bawingan, J.D. Awisan, D. Amilao, C.P. Pagaoa, D.D. Aquino, R. Doplah, U.P. Segundo (2016)	The Efficacy of Kiti-KitiX Larvicide against Aedes Aegypti under Field Conditions	Experimental	Mosquito population in 3 brgys in La Trinidad, Province of Benguet	Kiti-kiti X	Abate Temephos	Efficacy of Kiti-Kiti X larvicide against *aedes aegypti* under field conditions Decrease in Mosquito Larvae from containers	Inconclusive due to confounding factors Breteau index pre- to post-vector survey per barangay: Pre-vector Betag: 3 → 0 Puguis: 19 → 28 Wangal: 71 →	Wrong PICO and study design.

								33	
4	Theodore Aldrine Velasco Valte III (2013)	Evaluation of Calcium Hydroxide Formulation against the Pupae of *Aedes Aegypti* (Linnaeus) and Aedes Albopictus (Skuse) (Diptera: Culicidae)	Experimental (bioassay)	pupae of Aedes aegypti and Aedes albopictus; Crop Protection Cluster, UP Los Banos, Laguna	Kiti-kiti X (CaOH with cliniptilolite) - 1,350 ppm - 1,400 ppm - 1,450 ppm - 1,500 ppm - 1,550 ppm - 1,600 ppm - 1,650 ppm	None	%Mortality of *Aedes aegypti* and *Aedes albopictus* pupae Lethal concentration of Kiti-KitiX to kill 50% of the test specimen	5% to 95% pupa mortality Aedes aegypti: LC_{50} = 1489.14 ppm Aedes albopictus: LC_{50} = 1447.44 ppm	Wrong PICO and study design.
5	Antonietta P. Ebol DAP&E FPA Accredited Researcher, Exterminator, & Fumigator Center of Health Development Davao Region (2013)	Field Evaluation on the Residual Effectiveness of Kiti-KitiX against *Aedes Aegypti* Larvae	Field Evaluation	Wild strain Aedes Aegypti and Aedes albopictus larvae in Brgy. San Miguel, Digos City	Kiti-kiti X	None	Residual efficacy of Kiti-Kiti X against *Aedes Aegypti* Larvae mortality (Decrease in mosquito larvae from containers)	Brgy. A: 100% larval mortality Brgy. B: 30-100% larval mortality No conclusion in terms of number of cases Breteau index from baseline, during intervention, and post intervention Brgy. San Miguel A: 15 → 7 → 1 Brgy. San Miguel B: 22 → 6 → 4	Wrong PICO and study design.

-	Mayan U. Lumandas MD Virology Department Head	Activity of Kiti-KitiX against influenza	Laboratory Test Result						Wrong Population/Disease
Additional Data Requests									
6	Cordial, M. 2007	Multi-growth Promotant Supplementation of Broiler Diets	Feeding trial	(N=325) day-old Commercial broiler chicks	Multigrowth promotant (MGP) Treatment 1 - fed with basal starter and finisher diets Treatment 2 - fed with basal starter and finisher diets with 0.1% MGP Treatment 2 - fed with basal starter and finisher diets with 0.2% MGP	Body weight gain, food consumption, feed efficiency, dressing percentage and livability	NA (not used as larvicide)		Wrong PICO and study design.
7	Patriarca, S. 2008	Performance and Egg Quality of 50-Week Old Layers Fed with Additional Calcium	Laboratory Experiment	(N=100) individually caged 50-week old layers	Treatment 1 (n=20): basal layer diet (control) Treatment 2 (n=20): 1% ES or Source A Treatment 3 (n=20): 1.5% ES or Source A Treatment 4 (n=20): 1% CC or Source B Treatment 5 (n=20): 1.5% CC or Source B Note: Basal layer diet = 15% crude protein 2570 kcal/kg metabolize energy + 4% calculated amount of calcium from limestone ES = egg shield CC = classified calcium	Feed efficiency, feed consumption, egg weight, egg shell thickness, incidence of shell defects, livability, calcium intake	NA (not used as larvicide)		Wrong PICO and study design.

Note: Breteau Index (BI) = (no. of positive containers Aedes larvae/pupae / total no. of houses inspected) x 100
BI interpretation: BI ≥ 20, the area is high risk to dengue transmission; BI ≤ 20, the area is low risk to dengue transmission

Annex C. Administrative Order(AO) 303, AO 2014-0038, and AO 2019-0008 list of requirements for the renewal of Certification of Product Registration

List of Requirements		
AO 303	**AO 2014-0038**	**AO 2019-0008**
1. Application letter 2. Full List and amount of all the ingredients and materials used as component of the finished substances 3. Technical specification of all the ingredients used as component 4. Technical specification or description of the finished substance 5. Assay procedure of the active component 6. Five labels or specimens of the proposed label 7. Two markets or commercial presentation 8. Sufficient sample for laboratory analysis	1. Integrated Application Form 2. Notarized Declaration Form 3. Copy of Valid License to Operate 4. Product Composition 5. Safety Data Sheet* 6. Technical Specification of the Finished Product 7. Certificate of Analysis of the Finished Product 8. Manufacturing procedure 9. Complete Test Methods 10. Bio-efficacy Study* 11. Toxicity Study* 12. Stability Study 13. Substantiation of product claims, as applicable 14. Product Label 15. Finished commercial product per pack size	1. Integrated Application Form 2. Notarized Declaration Form 3. Valid LTO 4. Product Identity 5. Quantitative and Qualitative Composition of the Product 6. Technical specifications of the formulated product including tolerance for the active ingredients 7. Stability Study 8. Certificate of Analysis 9. Test Procedures/Methods 10. Safety Data Sheet* 11. Toxicity Data* 12. Bio-efficacy Data * 13. Human Exposure and Safety Data* 14. Environmental Data* 15. Product Label 16. Specification of Packaging

* Requirements also relevant to HTA

Annex D. List of WHO-prequalified Larvicides

Active Ingredient/Synergist	**Date of Prequalification**
Temephos	18 Apr, 2018
Pirimiphos-methyl	3 May, 2018
PDMS (Polydimethylsiloxane)	19 Dec, 2018
Diflubenzuron	3 May, 2018
Pyriproxyfen	7 Dec, 2017
Novaluron	19 Feb, 2018
Spinosad	21 Feb, 2018
Bacillus thuringiensis subsp. Israelensis strain AM65-52	19 Feb, 2018