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DEPARTMENT OF SCIENCE AND TECHNOLOGY



Calcium hydroxide + Clinoptilolite Larvicide for the Prevention of Dengue

Service Line

Evidence Summary

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Background

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).

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).

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). Currently, the WHO has pre-qualified eight larvicides based on its active ingredients and synergists and these are: Temephos, Pirimiphos-methyl, PDMS (Polydimethylsiloxane), Diflubenzuron, Pyriproxyfen, Novaluron, Spinosad and *Bacillus sphaericus* and *Bacillus thuringiensis subsp. israelensis* strain (WHO, 2023).

With the burden of dengue cases in the Philippines, the Department of Health (DOH) introduced the National Dengue Prevention and Control Program in 1993. The program components are: Surveillance, Case Management and Diagnosis, Integrated Vector Management (IVM), 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.

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 enumerated 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.

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, and 4) Support fogging/spraying only in hotspot areas where increase in cases is registered for two consecutive weeks to prevent an impending outbreak

Description, technical characteristics, and use of the health technology

The 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 and will serve as larvae traps, targeting locations, containers, or stagnant water that serve as breeding places of immature mosquito larvae, such as household and community-based targeting.

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

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 Calcium hydroxide + Clinoptilolite (*Kiti-KitiX*) against dengue?

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

Population	Entire Population, Filipino communities
Intervention	Calcium Hydroxide and Clinoptilolite (<i>Kiti-KitiX</i>) 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: <ul style="list-style-type: none"> - Population level reduction in dengue cases: Total dengue cases (any severity) Severe dengue cases Mortality due to dengue Safety <ul style="list-style-type: none"> - Any harmful effects (environmental and human health)

Final HTA Council Recommendation

The HTA Council **does not recommend** Calcium hydroxide + Clinoptilolite (*Kiti-Kiti X*) for government financing and inclusion in the list of larvicides to be used

by the Aedes Borne Viral Diseases (Dengue) Prevention and Control Program of the DOH **due to unavailability of sufficient clinical evidence on its efficacy, effectiveness and safety at this point.** The HTA Council suggests further studies to be conducted in order to provide the needed evidence that addresses its decision criteria based on the UHC Law.

Evidence which guided the Recommendation of the HTA Council

Responsiveness to Disease Magnitude and Severity

Burden of Disease

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.

Based on the PIDS-EDCS data from 2019 to 2023, there was a dramatic decrease by 81.0% in **reported cases** from 2019 to 2020. According to the PIDS 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).

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).

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 PIDS-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. 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.

In terms of annual dengue case fatality rate (CFR), the Philippines had a steady CFR of 0.40% from 2019 to 2021. 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 .

Research Question 1:

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

HTAC Judgment:

While limited data seem to show a decline in the number of deaths, case fatality rate, and incidence rate, dengue infection may still be considered a public health priority due to the following reasons:

- High morbidity and mortality among children ages 10-14 years old.
 - In the Philippines, dengue fever is in the top 10 leading cause of morbidity for 2015, 2016, and 2018 ([Philippine Health Statistics](#)). Acute hemorrhagic fever (ICD code 11: A97.0-A97.2) is the 16th leading cause of morbidity in 2022 ([Department of Health, 2022](#)).
 - In terms of mortality, dengue hemorrhagic fever or severe dengue is within the top 10 leading causes of mortality in children 1 to 15 years old in 2015 and 2016. Meanwhile, dengue fever ranked 9th and 4th in children aged 5-9 years old in 2015 and 2016, respectively. Dengue fever is not among the leading causes of mortality in the Philippines from 2017 to 2022 ([Philippine Health Statistics](#); [Philippine Statistics Authority](#))
- Morbidity among children may lead to lost days of work for parents/caregivers.
- CAR, which had the highest incidence rate of dengue in 2022 and 2023 ([DOH, 2019](#); [DOH -EB, 2023](#)), is also the region with 2nd highest percentage of Geographically Isolated and Disadvantaged Areas (GIDA) Barangays in 2019.
- There is a need to support and sustain program efforts in eradication of the mosquitoes infected with the dengue virus.

Further, there was a decrease in the number of cases, number of deaths, case fatality rate, and incidence rate observed in 2023 as compared to 2022. However, this may be

attributed to an incomplete report for 2023. ([DOH PIDS-EDCS Weekly Surveillance Report](#))

Efficacy, Effectiveness and Safety

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.

A systematic search of three databases was performed in duplicate on 10 January and February 1, 2024, yielding 179 studies that were further subjected to title and abstract screening. This screening resulted in only four studies on the safety of clinoptilolite. However, these four studies were also excluded upon full-text screening.

A review of the nominator submissions was also conducted in duplicate for the 7 studies in the dossier. To supplement the review, eight other documents submitted by the proponent were also screened as potential supplementary evidence, 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. However, these additional documents were ultimately excluded in the review due to lack of supporting studies.

Consultations with different relevant agencies were also conducted for this assessment. Among the consulted agencies were :

- the Philippine Food and Drug Administration (FDA) Center for Cosmetics and Household/Urban Hazardous Substances Regulation and Research (CCHUHSRR),
- 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.

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.

Research Question 2.1:

Is the Calcium hydroxide + Clinoptilolite larvicide (Kiti-KitiX) 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?

HTAC Judgment:

Vector control using larvicides is effective in dengue control. Unpublished field experiments on Calcium hydroxide + Clinoptilolite (*Kiti-KitiX*) have shown 30-100% larval mortality against *A. aegypti* (Ebol, 2013 [unpublished], Salazar, 2009 [unpublished]). However, there is no available clinical evidence that reported the efficacy or effectiveness of the Calcium hydroxide + Clinoptilolite (*Kiti-KitiX*) larvicide vs. previously utilized larvicides by the DOH and enhanced '4S' strategy in reducing dengue cases, severe dengue cases and deaths due to dengue.

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.

Research Question 2.2:

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

HTAC Judgment:

There are no available toxicology and environmental studies regarding the safety of the Calcium hydroxide + Clinoptilolite (*Kiti-Kiti X*) larvicide.

On the other hand, in terms of the individual components of Calcium hydroxide + Clinoptilolite (*Kiti-Kiti X*) there is no evidence of safety in humans. From animal studies and available Material Safety Data Sheet (MSDS) (e.g., US CDC NIOSH, PubChem), the National Poison Management and Control Center (NPMCC) concluded that individual components of Calcium hydroxide + Clinoptilolite (*Kiti-Kiti X*) appear to have dose-dependent toxic effects. In terms of environmental impact, the UP Manila College of Public Health Department of Environmental and Occupational Health (UPM-CPH-DEOH) 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.

Lastly, the CPR of the product expired on 17 April 2024. The FDA acknowledged that the evaluation criteria used in the previous authorizations of Calcium hydroxide + Clinoptilolite (*Kiti-Kiti X*) did not include human exposure safety data and environmental data. These will be required in the next Certificate of Product Registration (CPR) renewal which will follow the Administrative Order 2019-0008.

Review of Guideline Recommendations

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. The search was conducted on 17 January 2024.

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.

Research Question 2.3:

What are the current recommendations from country guidelines on the use of Calcium hydroxide + Clinoptilolite larvicide (Kiti-KitiX) against dengue?

HTAC Judgment:

There was no country guideline that recommended the use of Calcium hydroxide and Clinoptilolite (which are the components of Kiti-Kiti X larvicide) in their national program against dengue.

Further details on the methodology of the review, burden of disease data, guideline search and the overall assessment will be included in the Clinical Assessment Report for calcium hydroxide + clinoptilolite (Kiti-KitiX) to be published with the Final HTA Council Recommendation.

Due to unavailability of evidence of efficacy, effectiveness and safety, Calcium hydroxide + Clinoptilolite (*Kiti-Kiti X*) was no longer appraised against the remaining HTA decision criteria, namely, Household Financial Impact, Affordability and Viability, Cost-Effectiveness, and Ethical, Legal Social and Health Systems Impact.

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

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