Dengue Prevention and Control in the Post-COVID-19 Era: New Challenges and Role of Innovative Technology

APEC Health Working Group

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Asia-Pacific Economic Cooperation

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Contents

1. Introduction

This conference report is an output of an APEC- ASF Human Security Sub-Fund project of Health Working Group (HWG) from Session 1 of 2024, “HWG 102 2024A - Dengue Prevention and Control in the Post-COVID-19 Era: New Challenges and Role of Innovative Technology”. It is co-sponsored by Chile; Indonesia; Japan; Malaysia; Peru; the Philippines; Singapore; The United States; and Viet Nam.

In the post-COVID-19 era, the reopening of borders, coupled with global warming, has led to a resurgence of the global dengue fever epidemic.

Chinese Taipei proposes a project to provide APEC economies with a platform to share and discuss effective dengue prevention strategies. This project will strengthen sustainable and affordable control measures and clinical management for dengue prevention, thereby protecting people’s health.

Chinese Taipei to host a 2-day In-person Conference in April 2025. Conference activities include (1) interactive sessions and (2) a Field Visit to Nan-Mei Village in Tainan City

This project convenes a conference for epidemic prevention policy makers and officials, public health officials, border health officers, experts and private sectors (e.g. pharmaceutical industry).

This physical conference was held from 22-23 April 2025. Apart from the keynote speech, the 2-day in-person conference consisted of 4 main sessions: “Dengue Prevention and Control”, “Vector Surveillance and Control”, “Dengue Vaccine”, “New Technology Development in Vector Surveillance and Control”, and “Field visit to Nan-Mei Village, Tainan City”.

There were a total of 93 participants from 9 member economies. These member economies are Indonesia; Japan; Malaysia; Mexico; Singapore; Chinese Taipei; Thailand; The United States; and Viet Nam.

2. Topic-Based Summaries of Presentations

2.1 Keynote Speech 1 – Best Management Practices (BMP) for Technology Adoption in Dengue Vector Surveillance and Control

This keynote speech focused on how the Anastasia Mosquito Control District started the mosquito control program in 1948 and has expanded since 2003. The residents support the service as they have no local transmission or mutations. They have applied the "NO WATER NO MOSQUITOES" principle and adopted innovative technologies, including smartphone apps, AI, robotics, drones, GIS, modeling, prediction, eDNA, and pathogen detection. They have also developed AI-powered UVA (Drone), AI-powered crewless ground vehicle (UGV), and spray robots for spraying pesticides. The 22-year journey exemplifies Best Management Practices (BMP) in Florida, the United States. The speech proposed a multi-faceted approach that combines technology and research, enhances public engagement and education, and addresses operational and environmental challenges to effectively manage mosquito-borne diseases.

The detailed suggestions from the speech were as follows:

1. Strengthen Government and Inter-sectoral Collaboration:

- Increase Public Health and Mortality Response Capacity: Invest in resources and personnel to enhance the ability to respond to and manage mosquito-borne diseases.
- Establish an Economic Research Agenda: Create a focused research plan to streamline efforts and improve coordination across different sectors.
- Form Dengue Teams: Emulate successful models where different government agencies (e.g., Department of Health, Centers for Disease Control and Prevention (CDC), Environmental Protection Agency (EPA)) collaborate to strengthen monitoring, leverage innovative technology, improve public health value, and promote community involvement.
- Educate Politicians and the Public: Engage politicians to secure their support for policy-making and funding, and educate the general public to counter misinformation and foster compliance.

2. Leverage Technology and Research:

- Apply Lessons Learned from the COVID-19 Pandemic: Utilize the experience of the rapid development of COVID-19 diagnostic kits, drugs, and vaccines to accelerate dengue vaccine development.
- Continue and Expand Technology Adoption: Continue to integrate and expand the use of current technologies like smartphone applications, AI

public smart traps, SITellite GIS, computer modeling, AI public lab detection, environmental DNA/RNA, and pathogen detection.

- Invest in and Develop New Technologies: Continue to explore and implement innovative solutions like AI-powered UAVs (drones), UGVs, and spray robots.
- Support Research and Development: Continue to fund and engage in research, as evidenced by collaborations with universities and companies for technologies like vector IDX and eDNA sampling.
- Promote Biopesticides and Alternative Control Methods: Continue the development and deployment of methods like SIT (Sterile Insect Technique) and Attractive Targeted Sugar Baits (ATSB).

3. Enhance Public Engagement and Education:

- Promote Community Involvement: Encourage active participation from the community in vector control efforts.
- Address Public Misinformation: Counter false narratives about mosquito control by providing accurate information, emphasizing the low percentage of pesticide use compared to agriculture, and showcasing the benefits.
- Utilize Educational Centers: Leverage facilities like the mosquito museum and disease-control education center to educate the public.
- Conduct Public Education and Outreach: Continue programs like the 10 years of public education for *Wolbachia*-infected mosquitoes to build public acceptance and understanding.

4. Address Operational and Environmental Challenges:

- Innovate Container Inspection: Develop better methods or technologies to inspect all containers, given the challenge of "NO WATER NO MOSQUITOES" in environmentally complex areas.
- Adapt to Climate Change: Increase resources and research into how global warming, globalization, and transportation are creating new challenges for vector control.
- Enforce Standard Measures: Implement public health measures to change public behavior regarding vector control, such as mosquitoes and their breeding sites.
- Optimize Cost-Effectiveness: Rising labor and material costs highlight the need to identify more cost-effective solutions or to secure additional funding.

2.2 Session I – Dengue Prevention and Control

Below is a summary of the main points from the presentation *An Overview of Tainan City's Experience in Dengue Prevention and Control* is as follows:

The presentation provided an overview of how the Tainan City Government introduced seven strategies to prevent and control dengue fever in 2024. These strategies included restructuring the organization to strengthen team coordination, creating regional joint defense mechanisms to encourage collaboration between districts, setting up a monitoring system to enable early detection through designated clinics, employing vector surveillance to promote rapid response to mosquito breeding sites, providing active prevention measures to ensure public engagement, pushing for law enforcement to issue fines for neglected breeding sites, and raising public awareness to educate citizens on dengue prevention. Overall, the Tainan City government conducted successful dengue control through sustainable efforts devoted to advanced surveillance, community engagement, and international collaboration.

Below is a summary of the main points from the presentation *The Singapore Model for Combating Dengue*:

The presentation outlined how the Department of Infectious Diseases National Centre for Infectious Diseases (NCID) in Singapore has adopted a data-driven approach to identify the need for further improvements in developing rapid diagnostic tests and notification systems to help with timely case reporting and better manage the dengue outbreak. For example, the speaker shared that they identified that the dominant serotype in Singapore is DENV2, with periodic shifts between DENV2 and DENV1. With this information, they can better predict outbreak trends, implement vector surveillance and control, and monitor for potential outbreaks. Key factors in successful dengue prevention and control include enforcement and legislation, collaboration with the community, healthcare providers, and multidisciplinary agencies, research and implementation, and continuous improvements in current clinical care.

Below is a summary of the main points from the presentation *Strengthening Preparedness for Future Dengue Outbreaks in Malaysia: A Comprehensive Approach*:

The speaker introduced their economy’s strategic plan for dengue prevention control in 2022-2026, which serves as the current framework for dengue prevention in Malaysia. The strategic plan is built on three major pillars: optimizing the dengue surveillance system, ensuring accessibility to dengue diagnostic treatment and quality control initiatives, and consolidating efforts in dengue prevention and control. The three pillars include measures such as digitizing the dengue surveillance system, managing instant dengue healthcare delivery, and consolidating activities at the ground level, including outbreak response, collaboration, and implementation. At the cabinet level, Malaysia has a committee dedicated to combating dengue, which is chaired by His Excellency the Deputy Prime Minister. The *Wolbachia* mosquito operation has also been implemented. In conclusion, Malaysia has adopted a whole-of-economy strategy and approach to ensure that relevant agencies contribute to dengue surveillance and control.

Below is a summary of the main points from the presentation *The Thailand Model for Combating Dengue*:

The presentation outlined how Thailand took human-centered measures by practicing the four pillars: surveillance, prevention and vector control, case management, and risk communication. Since climate change may affect the adaptation of vectors, Thailand aims to enhance surveillance and emergency response, engage the community and network, and enhance public knowledge. In response to undetectable and unreported cases, Thailand has taken measures to strengthen forecasting and prevention through the development of dengue prediction models, vaccine research, and locally driven innovation. To address challenges such as inadequate patient care in hospitals and ineffective vector control, Thailand will strengthen communication and collaboration, create a sustainable disease prevention and control system, and boost community participation and social cooperation.

Key Takeaways from the Panel Discussion

This panel discussion provided insightful perspectives from Singaporean, Malaysian, and American speakers based on their experiences on the challenges and future directions of dengue prevention and control.

The speaker from Singapore initiated the discussion by addressing the significant differences and improvements observed with the adoption of WHO's 2009 severe dengue case definition compared to the 1997 criteria. The primary advantage highlighted for the 2009 criteria is its ease of use. Unlike the 1997 criteria, which required fulfilling four specific criteria for Dengue Hemorrhagic Fever (DHF) diagnosis, the 2009 criteria allow for a diagnosis of severe dengue if any single criterion is met. This simplified approach makes it more accessible for clinicians, leading to quicker and more accurate recognition of severe cases on the ground.

A crucial improvement in the 2009 criteria is its broader scope, particularly in recognizing severe organ impairment, which was not explicitly covered under the DHF classification of the 1997 criteria. Singapore, experiencing a higher burden of dengue in older adults, noted that this demographic often presents with severe organ involvement (e.g., neurological complications, myocarditis, severe hepatitis, HLH) rather than the pronounced hemorrhagic tendencies more common in younger patients. The 2009 classification better reflects these diverse clinical characteristics, enabling clinicians to identify and manage severe cases more effectively. The Malaysian experience with HLH post-dengue further underscores the importance of this expanded definition.

The 2009 criteria introduce "warning signs," which are invaluable for early stratification of patients needing more intensive care. In contrast, by the time a patient meets the 1997 DHF criteria, their condition is often already critical. The warning signs, such as abdominal pain and vomiting, allow for earlier intervention and potentially prevent progression to severe dengue. However, the speaker acknowledged a point of criticism regarding the 2009 classification: the potential for "over-calling" warning signs due to their general nature. This can lead to increased admissions of patients who may not require hospitalization, which requires careful clinical judgment to balance early intervention with efficient resource utilization.

Clinicians in Singapore have largely adopted the 2009 criteria, finding it more aligned with their clinical practice. While formal notification of severe cases in Singapore still sometimes references the DHF classification (1997 criteria), there's a growing alignment with the 2009 criteria in actual patient management. Regarding patient participation in dengue trials, the success of the *Wolbachia* program is: it is more challenging to recruit dengue patients due to its effectiveness.

The discussion then shifted to the *Wolbachia* prevention and control programs. The Malaysian speaker detailed their strategic approach to *Wolbachia* implementation. Key criteria for selecting localities include:

1. Hotspot Areas: Focusing on areas with high dengue incidence.
2. *Aedes aegypti* Predominance: Ensuring the chosen locality is predominantly affected by *Aedes aegypti*, as their program uses *Aedes aegypti Wolbachia*.
3. Community Participation: Crucially, community consent and active participation are prerequisites. Without community agreement, the program is not adopted.

A participant raised a question about Malaysia's use of dengue case reduction as a primary metric for *Wolbachia* program success, suggesting that mosquito reduction might be a more direct measure. The Malaysian speaker clarified that their ultimate aim is to reduce dengue cases. They compare pre-intervention case numbers with those two years post-intervention, observing a significant 45-100% reduction in cases. They explained that because their strategy is replacement (releasing both male and female *Wolbachia*-infected mosquitoes to replace the wild population) rather than suppression, the index (number) of mosquitoes is expected to remain relatively constant. Thus, case reduction is the more appropriate measure of success for their replacement strategy.

The Malaysian program prohibits fogging in localities where *Wolbachia* mosquitoes are released. This necessitates extensive community engagement to ensure residents understand the purpose of the program and refrain from using fogging, which could counteract the *Wolbachia* release. They do, however, continue with larviciding and other cleaning activities. This highlights the importance of public education and buy-in for the success of *Wolbachia* programs.

The speaker from the United States offered a broader ecological perspective on mosquito control. Emphasizing that mosquitoes are an integral part of the ecosystem, the US approach advocates for "best mosquito management practices" rather than attempting complete elimination. The speaker pointed out that many of the approximately 4,000 mosquito species do not transmit diseases and serve as a crucial food source for other animals.``

The US speaker stressed that control strategies should be data-driven and tailored to specific local situations, as exemplified by the varying *Aedes aegypti* habitats and control challenges in different economies like Singapore and Thailand.

In response to a critical question raised about rapid dengue diagnosis, especially how to manage potential co-infections with Zika or Chikungunya, the Singaporean speaker explained that while their current incidence of Zika and Chikungunya is low, clinicians remain vigilant. Clinical suspicion guides further testing. Some labs, like in Tehran and Iran, employ multi-PCR tests for dengue, Zika, and Chikungunya simultaneously. For surveillance purposes, Singapore also conducts pan-flavivirus PCR on clinically suspected but NS1-negative patients, though this is not typically for immediate clinical use.

A question about homeowners using over-the-counter aerosol products that could kill *Wolbachia*-infected mosquitoes was posed. The Singaporean speaker, whose economy adopts a suppression approach for *Wolbachia*, reiterated the paramount importance of community engagement. Thorough education is needed to ensure residents understand the program and refrain from killing the released mosquitoes, even though they might see more mosquitoes initially. Cases of private pest control operators fogging within *Wolbachia* release areas do occur, underscoring the ongoing challenge of maintaining 100% compliance. The Malaysian speaker echoed this sentiment, sharing an anecdote about public frustration over seeing more mosquitoes despite the program, emphasizing that constant communication and reassurance are vital for program sustainability and public acceptance. The challenge lies in convincing the public that the temporary increase in mosquito presence is part of a beneficial long-term strategy for disease control.

2.3 Session II – Vector Surveillance and Control

Below is a summary of the main points from the presentation *Status of Insecticide Resistance in Aedes Mosquitoes Across Asia*:

The extensive and indiscriminate use of insecticides has led to the development of insecticide resistance. There are physiological resistance and behavioral resistance, and both in vivo and in vitro methods should be tested with either adult mosquitoes or larvae. Most importantly, biochemical and metabolic inhibitors should be used to dissect the exact mechanism for the respective resistance in addition to molecular characterization.

There is an urgent, unmet need for an insecticide-resistant database repository in Asia, since without the result, whether resistance exists can be indicated is not known, and this could become a potential hidden challenge for vector control and surveillance. This repository would assist vector control departments in sharing standard models among economies such as, such as Cambodia; China; Malaysia; Myanmar; Singapore; and Thailand. All these places are sharing models. However, the US only shares data on resistance mechanisms unless it is big data. It is just bilateral sharing between individual economies, not through a central database. Using synergies and other modes of action should be considered.

Below is a summary of the main points from the presentation *Dengue Vector Surveillance and Climate-Based Distribution Projections in Chinese Taipei*:

The speaker presented her colleague's work on Dengue Vector Surveillance and Climate-Based Distribution Projections in Chinese Taipei, which monitored how climate change has affected *Aedes* behavior and habitation. The presentation demonstrated that the *Aedes aegypti* remains limited to areas south of the tropic of cancer and below 1,000 meters in altitude. At the same time, *Aedes albopictus* has an established itself at altitudes above 2,000 meters, exceeding its previously recognized upper limit. Therefore, reinforcing the active dynamic surveillance system is critical in the post-COVID-19 era. Dengue is no longer just a tropical issue. It has become a global concern. Temperature change is a critical environmental factor in determining the range of dengue vector distribution. As with global warming, vectors like *Aedes aegypti* and *Aedes albopictus* are expanding into new regions. They are expected to spread to every continent except Antarctica.

Below is a summary of the main points from the presentation *Insecticide Resistance and Range Expansion of Dengue Vectors in Japan: Public Health Challenges and Control Strategies*:

In Japan, three prevalent mosquito species, *Aedes aegypti*, the *Culex pipiens* complex, and *Culex tritaeniorhynchus*, are major vectors of vector-borne diseases. Researchers have been studying the distribution of *Aedes albopictus* for over two decades. This research revealed that *Aedes albopictus* thrives in regions with an annual average temperature of 11 degrees Celsius or higher. As temperatures rise, this species of mosquitoes has been progressively expanding its range northward across Japan.

A new vector control manual was developed after significant outbreak in 2014. This comprehensive guide covers crucial areas such as surveillance, insecticide application, and community engagement, providing essential support to local governments and partners. To enhance overall vector control capability, annual short training courses on vector mosquitoes are provided for local government officials. Since the outbreak, these efforts have expanded to include large-scale, free training exercises, attracting participation from various organizations including local governments, the Ministry of the Environment, research institutes, and pest control companies, highlighting the importance of collaborative mosquito control.

Despite these efforts, a concerning development emerged in 2022: the identification of a 1016-Valine-to-Glycine mutation in *Aedes albopictus* in Tokyo, which confers high resistance to pyrethroid insecticides. By 2023, testing of over 700 *Aedes albopictus* specimens revealed that approximately 1.5% carried this resistance gene. While the current ratio is less than 1%, its persistence suggests that this early resistance could significantly compromise future mosquito control strategies.

Furthermore, while *Aedes aegypti* is not native to Japan, repeated detections at international airports like Narita and Haneda are a cause for concern. Although the numbers collected are not large, genetic analysis of these invasive *Aedes aegypti* has shown that most are also pyrethroid-resistant.

Aedes albopictus is spreading in Japan and becoming increasingly difficult to control due to developing pyrethroid resistance. The repeated detection of pyrethroid-resistant *Aedes aegypti* at international airports also poses a risk. Effective mosquito control in Japan demands robust scientific research and sustained collaboration among diverse stakeholders.

Below is a summary of the main points from the presentation *Assessment of Pyrethroid Resistance in Vector Mosquitoes: Current Status and Challenges*:

The presentation outlined TCDC's strategies to control dengue transmission from vectors: (1) TCDC will establish relevant surveillance methods and criteria, such as a Breteau Index. (2) TCDC cooperates with local environmental and health bureaus, which will remove breeding sites, conduct surveillance, and send data weekly to TCDC. (3) Chemical control will be applied to the patient's house and the nearby environment whenever a dengue case is confirmed. Thus, insecticide will continue to be used and inevitably cause insecticide resistance. The presentation also showcased how TCDC has developed allele-specific qPCR (ASQ) and the Recombinase Polymerase Amplification combined with Lateral Flow Assay (RPA-LFA) technology to shorten the mutant detection time and to be applied rapidly in the field. Moreover, these methods have become useful tools for real-time monitoring of molecular markers of voltage-gated sodium channel (VGSC) mutations resulting from insecticide resistance for vector surveillance and control.

Key Takeaways from the Panel Discussion

In this panel discussion featuring speakers from Japan; Chinese Taipei; and the United States, critical aspects of mosquito surveillance, insecticide resistance, and innovative control approaches for *Aedes aegypti* and *Aedes albopictus* were highlighted. Key themes that were emphasized in the panel discussion were the importance of molecular and biochemical analyses, growing concerns regarding indoor insecticide spraying, and the necessity of a multi-faceted strategy for resistance management.

1. Understanding Mosquito Movement and Origin:

- Molecular Surveillance: The National Health Research Institutes (NHRI) in Chinese Taipei employs molecular analysis to track mosquito populations. Examining the genetic background of *Aedes aegypti* and *Aedes albopictus* collected from different administrative regions can determine the origin of mosquito strains and their movement patterns. For example, a recent finding indicated that *Aedes aegypti* found in Beigang likely originated from Kaohsiung, suggesting human transport as a primary driver of their spread rather than local establishment.
- Significance: This type of genetic analysis, while not yet routine, is crucial for understanding mosquito dispersal and informing targeted control efforts. It helps differentiate between locally established populations and those introduced through human activity, which can significantly impact intervention strategies.

2. Combatting Insecticide Resistance: A Multifaceted Approach:

- Beyond KDR: The discussion emphasized that insecticide resistance is a complex issue extending beyond the widely studied kdr (knockdown resistance) gene. Metabolic resistance, particularly involving P450 enzymes, is often more prevalent in pyrethroid resistance.
- Biochemical Assays are Key: A significant challenge highlighted is the current trend where researchers are more proficient in DNA-based analyses than protein work. However, biochemical assays (e.g., for enzymatic activity like P450) are crucial for comprehensively understanding resistance mechanisms. These assays are relatively inexpensive and can be performed quickly, providing vital data for developing effective resistance management strategies. There's a strong call to push for increased monitoring of resistance using biochemical assays.
- Synergists: The potential of incorporating synergists, such as Palladium(II)oxide (PdO) with pyrethroid insecticides, was mentioned as a promising strategy to overcome P450-mediated resistance.
- Larviciding as a Primary Strategy: A strong consensus emerged on the effectiveness and importance of larviciding, especially using temephos. Resistance to organophosphates like temephos remains relatively low compared to pyrethroids, making larviciding a sustainable and impactful control method.
- Integrated Approach: Effective resistance management requires combining in vivo testing on adult mosquitoes with a thorough understanding of all potential resistance mechanisms, not just kdr.

3. Challenges and Future Directions in Resistance Detection and Control:

- Rapid Detection Kits: While rapid detection kits for resistance gene analysis are being developed, linking resistance data to precise insecticide concentrations and validating these findings through field tests is still an ongoing effort.
- Pesticide Data Collection: The importance of collecting and analyzing data on chemical pesticides used by local governments was deemed crucial for resistance management, although challenges in obtaining comprehensive "actual" field data exist.
- Linking Mutation and Resistance: Research in Japan is focused on how to link specific genetic mutations to resistance phenotypes through special selection techniques and the establishment of mosquito colonies with specific markers. This allows for more targeted biochemical and bioassay testing.
- Behavioral Resistance: Behavioral resistance, where mosquitoes avoid treated areas, is a growing concern. Two main methods for detection were discussed: the WHO method and a high-throughput assay developed at

Kasetsart University, Thailand. These methods involve observing mosquito avoidance behavior in response to insecticides.

4. Concerns Regarding Indoor Spraying and Environmental Impact:

- Pyrethroid Risks: Mounting evidence, particularly since 2020, has highlighted the adverse health impacts of pyrethroids on humans, including increased risk of cardiovascular diseases and neurological dysfunctions, especially in young children. Regulatory bodies, like the California Department of Pesticide Regulation, are closely monitoring the indoor use of pyrethroids, potentially leading to restrictions on over-the-counter products.
- "Forever Chemicals" (PFAS): Many pyrethroids, including commonly used ones like lambda-cyhalothrin and cypermethrin, are PFAS compounds. PFAS are persistent "forever chemicals" that accumulate in the environment and human bodies (an estimated 95% of Americans have PFAS in their blood). With Europe likely moving towards phasing out PFAS soon and the US EPA increasing monitoring, there is significant concern about the long-term environmental and health consequences of using such insecticides.
- Minimizing Indoor Treatment: Given these concerns, the panel strongly advocated for minimizing indoor insecticide treatment, especially thermal fogging with pyrethroids. Outdoor larviciding and targeted treatment as absolutely required were emphasized as preferred alternatives.

2.4 Keynote Speech 2 – Dengue Vaccine Update Review & WHO recommendations

This keynote speech gave a thorough review of the dengue vaccine and the current practices and directions of WHO recommendations on TAK-003 for specific serotypes. The TAK-003 vaccine, which uses a live attenuated DENV2 serotype as its backbone, was used to target all four dengue virus serotypes. Research priorities include post-marketing to generate more precise estimates of the vaccine effectiveness against serotypes, especially 3 and 4, monitoring the rate of hospitalization, pregnancy incidence, birth outcome, and assessing the safety and immune response, especially among the elderly. Programmatic consideration to optimize the impact of the vaccine would need to be delivered to school-going children and adolescents with the assistance of emergency care; co-administration with other vaccines like HPV and fitness bacterial vaccines may help optimize coverage and reduce overall operational costs. Anaphylaxis has been reported to be managed and closely monitored. Safety and circulating single types are important during the launch of the program.

The detailed suggestions from the speech were as follows:

1. The WHO recommends routine immunization with TAK-003 in areas with high dengue transmission, particularly for children aged 6-16, administered one or two years before peak hospitalization age. It is not recommended for children under six or in low transmission settings until DENV3/DENV4 efficacy in seronegative individuals is fully assessed. Pre-vaccination screening is generally not advised for public health programs.

2. TAK-003 can be co-administered with yellow fever, Hepatitis A, and HPV vaccines. While effective, caution is advised for individuals with a history of anaphylaxis to vaccine components, pregnant or immunocompromised individuals, and those with HIV. Real-world data from Brazil indicated 16 anaphylaxis cases (4.4 per 100,000 doses) during initial rollout. Continuous high-quality surveillance and post-marketing studies are vital to monitoring vaccine effectiveness and safety, especially concerning DENV3/DENV4 serotypes and in vulnerable populations like the elderly.

3. Persons living in non-endemic economies who have previously been infected with any of the four dengue virus serotypes (e.g., during prior travel to dengue-endemic areas) may benefit from TAK-003 vaccination. The goal is to prevent a second dengue infection, which can often be more severe. For frequent travelers, long-term travelers, migrants, and long-term expatriates are identified as groups who might particularly benefit from the vaccine. While pre-vaccination screening is generally not recommended for public health programs, travelers must be informed that the vaccine may offer limited protection against DENV3.

4.The programmatic consideration to optimize the impact of the vaccine would need to be delivered to school-going children and adolescents with the assistance of emergency care; co-administration with other vaccines like HPV and Hepatitis A and B vaccines may help optimize coverage and reduce overall operational costs. Anaphylaxis has been reported to be managed and closely monitored. Safety and circulating single types are important during the launch of the program.

2.5 Session III – Dengue Vaccine

Below is a summary of the main points from the presentation *The Development of TAK-003 and its Role in the Region/Global Dengue Prevention Efforts*:

The speaker demonstrated TAK-003 protective efficacy against symptomatic dengue infection and hospitalization. The Indonesian Pediatric Society has recommended the dengue vaccine. The Indonesian Technical Advisory Group for Immunization has reviewed all the data, including disease epidemiology, vaccine safety, efficacy, economic evaluation of vaccine, feasibility program, vaccine acceptability, and other considerations, and then has concluded that the dengue vaccine is a priority between 2025 and 2029. Three districts in Indonesia have included the dengue vaccine into its vaccination programs, including school-based immunization initiatives. They found that circulating serotypes differ from region to region and island to island in Indonesia. Combinations such as serotypes of 1 and 3, 2 and 3, or even three serotypes during a single infection can be exhibited. Cost-effectiveness analysis of the study suggests a high public health impact and a potential 60% to 66% reduction in the DALYs, and the economic impact will also be perceived.

Below is a summary of the main points from the presentation *Update of Dengue Vaccine Development at the US NIH*, as follows:

The presentation gave a historical and detailed view of dengue vaccine (TV003/TV005) development at the US NIH and future highlights.

Moreover, the speaker emphasized how age groups for vaccination should be carefully examined before vaccination based on the clinical trials in Argentina; Brazil; China; Chinese Taipei; and other economies. Particular in Chinese Taipei, after several years of follow-up, there is a significant incidence in adults older than 50. No substantial evidence supports the use of this vaccine in the elderly population. However, most of these clinical trials have an upper age limit of 60 years old. Chinese Taipei has initiated a phase 2 study on TV005 targeting the 50 to 70-year-old population. This study is focused on evaluating safety and immunogenicity. There are 254 participants in this study, and the study results are under evaluation. The goal is to develop a dengue vaccine that is effective and safe for individuals of all serostatuses and age groups.

Key Takeaways from the Panel Discussion

This panel discussion, featuring speakers from Indonesia; Chinese Taipei; and Thailand, delved into the complexities surrounding dengue vaccine development, the incidence of post-vaccination anaphylaxis and strategic considerations for public health interventions.

1. Re-evaluating Post-Vaccination Anaphylaxis Incidence:

- The moderator opened by addressing the surprisingly high reported incidence of anaphylaxis (67 per million) in an early-phase study on vaccination conducted in Brazil. This figure significantly deviates from the typically expected 1 per million doses across all vaccine types. A crucial lesson drawing from past experiences with HPV and COVID-19 (AZ and mRNA) vaccines is the importance of careful data cleaning and the application of a stringent definition of anaphylaxis.

- Psychosomatic Reactions vs. True Anaphylaxis: Many reported cases initially suspected as anaphylaxis, especially after COVID-19 vaccination, were later found to be psychosomatic reactions, such as fainting attacks, driven by anxiety related to injections. This highlights the need for robust diagnostic criteria to differentiate true anaphylactic events from other adverse reactions.
- Implication: This re-evaluation of data suggests that the true incidence of anaphylaxis after vaccination is considerably lower, estimated closer to 2 to 2.8 per million, aligning more with general expectations. This understanding is vital for managing public perception and vaccine hesitancy.

2. The Persistent Challenge of Dengue Fever Vaccines and Antibody-Dependent Enhancement (ADE):

A major theme of the discussion revolved around the enduring difficulty in developing a highly effective dengue vaccine, primarily due to Antibody-Dependent Enhancement (ADE).

- Understanding ADE: ADE occurs when pre-existing, non-neutralizing antibodies (either from a previous infection or vaccination) bind to a virus. This forms immune complexes that, instead of neutralizing the virus, antibodies facilitate its entry into host cells via Fc receptors, leading to enhanced infection and often more severe disease.
- Dengue's Unique Complexity: Unlike some other viruses where ADE can be avoided by using pre-fusion forms of antigens (as seen in current RSV and COVID-19 vaccines), the specific protein antigen responsible for ADE in dengue fever remains elusive.
- Precursor Membrane (PrM) and Envelope Protein (E): The speaker from Indonesia highlighted the precursor membrane (PrM) as a potential target for neutralizing antibodies and theoretically implicated in ADE. Both PrM and the envelope protein (E) are crucial for neutralization in dengue. The challenge lies in designing a vaccine that induces neutralizing antibodies for all four dengue serotypes without simultaneously inducing enhancing antibodies for others.
- Long-Term Monitoring: A critical message from the Thai speaker was that initial study results cannot guarantee the absence of ADE in the long term. Therefore, continuous, long-term surveillance of hospitalized cases following vaccination is essential if a dengue vaccine is widely implemented, as recommended by the WHO.
- Balanced Immune Response: The consensus is that a good dengue vaccine must induce equally balanced immune responses against all four serotypes. This balance is incredibly difficult to achieve and is considered the most challenging aspect of dengue vaccinology. The same applies to as with other complex viruses like Zika.

3. Serostatus and Vaccine Efficacy/Safety:

The discussion explored why seronegative vaccine recipients (individuals never previously exposed to dengue) might experience different outcomes, including potentially higher risks of ADE.

- "Primary-like" Infection in Seronegatives: For seronegative individuals, vaccination with a live-attenuated vaccine acts like a primary infection. If they are later exposed to a different wild-type dengue virus, this subsequent exposure can act as a "secondary" infection, which is known to cause more severe dengue, potentially due to ADE.
- Immune Response Intensity: One theory suggests that seronegative individuals, after vaccination, might not achieve an immune response (including T-cell response) strong enough to effectively neutralize a subsequent natural infection, making them more susceptible to the enhancing effects of sub-neutralizing antibodies. This aspect is crucial for understanding dengue pathogenesis and future vaccine assessment.

4. Current Landscape of Dengue Vaccines:

The panel discussed the current availability, costs, and limitations of dengue vaccines on the market.

- CYD-TDV (Dengvaxia®): This vaccine is no longer in production. Its use required pre-screening for dengue seropositivity due to the risk of severe dengue in seronegative individuals after vaccination. This screening made its implementation costly and logistically challenging.
- TAK-003 (Qdenga®): This vaccine is currently available and generally recommended for seropositive individuals. Its efficacy has shown limitations against DENV-3 and DENV-4 in seronegative individuals. The decision to implement TAK-003 needs to depend on an economy's specific context, considering the local seroprevalence and the endemicity of different DENV serotypes.
- TV005 (developed by NIH): This vaccine is still under development but shows potential, particularly in improving side effects like rash compared to earlier formulations. The NIH is exploring the possibility of licensing manufacturing to endemic economies to lower prices and facilitate vaccination campaigns.
- The "Perfect Vaccine" Remains Elusive: The Indonesian speaker noted that a "perfect vaccine" free of all limitations has yet to be achieved for dengue. Each available vaccine has its strengths and limitations, necessitating careful consideration for public health implementation.
- Cost-Benefit Studies: Cost-benefit analyses are crucial for deciding on vaccine implementation, especially in resource-limited settings.

5. Vaccine Side Effects and Considerations:

Rash Incidence: The incidence of rash was noted as a common side effect, particularly with earlier vaccine formulations like TAK-003. Studies suggest that the occurrence of rash might be influenced by an individual's baseline serostatus. TV005 has shown improvements in this regard.

6. Vaccine Use in Outbreak Response:

- A critical question was whether dengue vaccines are suitable for outbreak response, especially in areas with sporadic cases.
- Lack of Data for Outbreak Use: The primary reason against recommending current dengue vaccines for outbreak response is the lack of clinical trial data supporting their effectiveness in this specific context.
- Dosing Schedule: TAK-003, for instance, requires two doses administered three months apart. In an acute outbreak situation, by the time the second dose is given, the outbreak may have already subsided.
- Immune Response Timeline: While the initial immune response after the first dose might be good, there's no conclusive data to show immediate protective efficacy during an ongoing outbreak.
- Challenges in Differentiation: Using a vaccine during an outbreak could make it difficult to differentiate between vaccine-induced viremia/rash and symptoms caused by natural infection, complicating case management and surveillance.
- Emergency Situations: While acknowledging that vaccines are sometimes deployed in emergencies without complete data (e.g., COVID-19 vaccine for the elderly during the pandemic), the panel emphasized the current lack of evidence for dengue vaccine use in outbreaks.

2.6 Session IV – New Technology Development in Vector Surveillance and Control

Below is a summary of the main points from the presentation *Project Wolbachia – Singapore: Wolbachia-Aedes Mosquito Suppression Strategy*:

The speaker presented the successful case of the *Wolbachia* project in Singapore, where the combined use of *Wolbachia-Aedes* mosquitoes, traditional vector control, and continued vigilance is used to monitor the effects of Project *Wolbachia* under the densely populated city-state. Singapore experienced high dengue cases in 2024. There were 13,000 cases, a 37% increase from 2023. With Project *Wolbachia*, traditional vector control, and continued vigilance, the mid-year surge in dengue cases has been subdued. Singapore plans to monitor the effects of the Project *Wolbachia* as household coverage increases over the years to see how it will impact the number of dengue cases.

Below is a summary of the main points from the presentation *Wolbachia Replacement Strategy: A Promising Intervention for Dengue Control in Indonesia*:

The speaker presented how they utilized the *Wolbachia* replacement strategy to successfully reduce the fogging rate and to demonstrate dengue control. The project began with the release of eggs. Before the trial, they saw more frequent outbreaks with higher peaks. After the trial, the case trends were even flatter during 2023 and 2024. After they completed the release, positive cases were substantially lower because they also deployed mosquitoes with *Wolbachia* in the control area after the trial. Insecticide fogging was also much lower. After seeing the result, the Ministry of Health insisted on including it in daily control in Indonesia. The project involved extensive community engagement, including reaching out to the households and the community leaders and identifying which households agreed to receive the packet. The *Wolbachia* technology has demonstrated promising public health values and self-sustaining resilience and has the potential to be incorporated into public health infrastructure to protect against dengue, Zika, chikungunya, and yellow fever.

Below is a summary of the main points from the presentation *Implementation of Radiation-Based Sterile Insect Technique (SIT) Against Dengue Vector, Aedes aegypti, in Indonesia: Progress and Challenge*:

The speaker showcased how they have implemented a radiation-based sterile insect technique (SIT) against *Aedes aegypti* and is progressing into phase 2 deployment. They irradiated the male with ionizing radiation and released the male insects in large numbers to the field to compete with wild-type males for mating with females and become infertile. Before releasing the sterile males, the team conducted the Ovitrap surveillance based on the Chinese Taipei's experience. They further conducted a Mark release recapture (MRR) study to estimate the mean distance traveled in the field. Later, they used the sterile insect technique combined with integrated vector management.

Below is a summary of the main points from the presentation *Practical Experiences in Using Digital Technology for Vector Prevention and Control*:

The speaker demonstrated how they designed the digital Dengue application to overcome the extensive use of paper by utilizing an interface for the first-line staff a coordination interface for the central control teams, and an admin panel for the admin to control every section, get information, and do historical research. Overall, it increased efficiency, improved operation and coordination, reduced the phone line burden, and enhanced public health efficiency for dengue prevention and control.

Below is a summary of the main points from the presentation *The Development of a Climate-Based Prediction Model for Dengue Epidemics*:

The speaker shared a climate-based prediction model for dengue epidemic by leveraging the power of statistical modeling, mathematical modeling, machine learning, deep learning, and artificial intelligence technology in response to the rising challenges of dengue surveillance and control owing to global climate change. With this research, they aim to implement an early warning system in the context of climate change, indicate a proper probability-based response prediction model, and evaluate the necessity. AI and deep learning techniques may help to compensate for missing data. However, low-income economies may face challenges in applying sophisticated statistics and techniques to deploy the early warning system, which may cause inequality. Collaboration and support from high-tech economies can help low-income economies better prepare for the decade of AI.

Key Takeaways from the Panel Discussion

This panel discussion, featuring speakers from Indonesia; Singapore; Chinese Taipei; and Thailand, provided a comprehensive overview of innovative mosquito control strategies, the challenges of implementing them, and the critical role of data in public health. The discussion primarily revolved around *Wolbachia*-based methods, their integration with traditional approaches, and the development of robust climate-based prediction models.

1. Evolving Mosquito Control Strategies: Suppression, Replacement and SIT

The panel explored different strategies for mosquito control, particularly *Wolbachia*-based methods, and their suitability in various local contexts.

- Singapore's *Wolbachia-Aedes* Mosquito Suppression Strategy:
  - Method: Singapore employs male *Wolbachia*-carrying mosquitoes to suppress wild *Aedes* populations. This requires continuous, high-pulse releases of male mosquitoes.
  - Challenges: The primary challenge is the cost of continuous releases, though cost-benefit analyses indicate the benefits outweigh the expenditure.
  - Adaptation for Sustainability: To improve long-term sustainability, Singapore is dynamically adjusting its release strategy. They are evaluating both the mosquito index and mosquito population data from the Gravitrap surveillance system to determine whether certain release areas still require *Wolbachia-Aedes* mosquitoes deployment. This can allow resources to be reallocated to other areas. This dynamic approach aims to optimize resource allocation and ensure the program's viability.
- Indonesia's *Wolbachia* Replacement Strategy:

- Method: Indonesia focuses on a *Wolbachia* replacement strategy, under which *Wolbachia*-infected mosquitoes are released to establish a permanent population that is less capable of transmitting dengue.
- Indonesia's Rationale for Replacement Strategy: Given Indonesia's vast size and the widespread endemicity of dengue (affecting almost all 540 districts, with plans to scale up in 200 high-endemic districts), the replacement method is deemed more cost-effective and manageable than the high-resource suppression method. The sheer scale of the economy makes the continuous, high-pulse releases required for suppression economically unfeasible for the government. The Indonesian speaker highlighted that while Singapore's suppression strategy is less ecologically risky and manageable for a small, resource-rich economy, it is not suitable for Indonesia's context. This emphasizes that successful mosquito control strategies are highly dependent on a given economy's geographical size, resources, and environmental factors.

- Current Progress of SIT in Indonesia:
  After the successful small-scale implementation in Banu City, Indonesia is moving to randomized controlled pre-operational trials to assess both entomological (mosquito population reduction) and epidemiological (daily case reduction) endpoints. Artificial barriers are used in densely urban areas to prevent mosquito migration.

2. Integrating *Wolbachia* and SIT Methods with Traditional Vector Control:

A key concern raised was the coordination between *Wolbachia*-based methods and traditional approaches like chemical spraying, which could inadvertently harm released *Wolbachia* mosquitoes.

- Singapore's Coordination: Singapore prioritizes avoiding chemical intervention in *Wolbachia* release sites unless there is a massive dengue outbreak. Even then, strict coordination (e.g., scheduling *Wolbachia* releases on Monday/Thursday and chemical spraying on Wednesday) ensures that released mosquitoes are not unnecessarily killed. Their success in suppression has also led to lower dengue cases, reducing the need for chemical intervention.
- Indonesia's Approach to Coexistence:
  - Complementary Intervention: Indonesia frames *Wolbachia* release as a complementary intervention to existing vector control activities. Communities are not asked to change their usual insecticide use.
  - No Differential Selection: The crucial point is that insecticides do not differentially select *Wolbachia*-carrying mosquitoes from wild mosquitoes. When *Wolbachia* mosquitoes are released, their background insecticide resistance is matched to the wild population. This ensures that insecticides impact both *Wolbachia*-infected and wild

mosquitoes similarly, leading to a overall reduction in the mosquito population, including those carrying *Wolbachia*.

- SIT and Population Density: For suppression strategies like SIT, releasing sterile males is most effective when the wild mosquito population is low. If an outbreak occurs and density is high, additional treatments are needed to reduce the population before SIT can be effectively applied.

3. Application of *Wolbachia* and SIT in Outbreak Response:

The discussion addressed whether *Wolbachia* or SIT strategies could be effectively applied during dengue outbreaks, especially in economies like Chinese Taipei with periodic epidemics.

- Challenges in Outbreak Response:
  - Cost and Logistics: The cost of deploying *Wolbachia* during an outbreak is high, and identifying large, active dengue clusters for targeted deployment is challenging.
  - Delayed Efficacy for Suppression: Suppression methods cannot affect *Aedes* mosquitoes in their immature stages at the time of release. There's a delay between release and observable impact, as newly hatched mosquitoes need to mature to transmit the virus. If an outbreak is already in full swing, the immediate impact of suppression will be limited, with effects felt later.
  - Replacement Method's Advantage: The replacement method (Indonesia's strategy) offers a potential advantage in outbreaks as the *Wolbachia* population is already established and persistent, potentially defending against the peak of the outbreak. Indonesia's experience shows lower outbreak peaks in areas with *Wolbachia* replacement.
- Lack of Data: There is currently no definitive data or established protocols for using *Wolbachia* or SIT specifically for immediate outbreak response. Singapore plans pilot trials to study *Wolbachia* deployment in hot spots during cluster formation to assess its impact on outbreak severity.

4. Climate-Based Models and Data Quality for Disease Prediction:

The panel discussed the development of climate-based models for risk mapping and early warning systems, emphasizing the critical role of data.

- Challenges with Climate Change: Building robust predictive models under highly variable climate conditions (due to climate change) is challenging.
- AI and Data Input: Thailand is using neural networks (AI) for climate-based prediction models, showing promising results with low error rates. However, the effectiveness of AI models is entirely dependent on the quality, completeness, and accuracy of input data.

- Importance of Data Collection: The speakers from Chinese Taipei and Thailand stressed that data is more important than any technology for accurate predictions, especially in AI. There's a significant need for comprehensive and detailed data collection, particularly in developing economies, to maximize the benefits of AI in health prevention tools.
- Indoor Microclimate Considerations: A participant from Chinese Taipei highlighted that climate models should cautiously consider indoor microclimates, as indoor temperatures and breeding resources (not always correlated with outdoor rainfall) can significantly differ from outdoor conditions, especially in economies with indoor heating systems.
- Risk Communication: Despite limitations, such climatic-based models can serve as valuable early warning systems for risk communication, providing evidence-based information to prompt public action. Integrating human behavior into these models remains a significant challenge.

3. Field Visit to Nan-Mei Village in Tainan City

The field visit to Nan-Mei Village and its surrounding areas showcased community-based dengue prevention efforts, including the elimination of mosquito breeding sites and improvements in environmental management through resident engagement and practical vector control measures.

Nan-Mei Village, located in Tainan's Central-Western District, is a densely populated area renowned for its numerous historical sites and temples, which attract large numbers of international tourists. The combination of high population density and constant visitor traffic significantly heightens the risk of dengue transmission in the area.

During the visit, as part of a broader dengue prevention strategy, a series of educational activities were introduced. Among these was a VR-integrated digital interactive learning program designed to raise awareness among younger generations. This innovative course transforms students into "dengue prevention cadets," training them to identify and eliminate mosquito breeding sites through gamified, experiential learning. The program's engaging design enhances students' understanding of dengue prevention concepts and strengthens their practical skills, reinforcing the vital role of education in sustainable vector control.

In addition to educational outreach, the hosting team also demonstrated grassroots innovation in operational practices. To address the challenges of vector surveillance in hard-to-access locations such as rooftops and tree holes, they developed a multifunctional inspection tool—the "Roof Gutter Stick." Constructed by repurposing everyday household items, including extendable mops, bathroom accessories, and convex mirrors, the tool enables efficient inspection and cleaning of rooftop gutters, along with the immediate application of larvicide. It exemplifies the principle of upcycling waste into functional resources while promoting environmental sustainability.

This field visit not only highlighted Tainan City's multifaceted achievements in community engagement, educational innovation, and dengue prevention tool development, but also served as a valuable platform for knowledge exchange and mutual learning with APEC economies.

4. Integrated Overall Summary

The panel discussions across these four sessions highlighted a comprehensive and evolving strategy for managing dengue, emphasizing adaptability, technological integration, robust data utilization, and collaborative public health efforts. Experts collectively outlined current best practices and future directions, emphasizing a shift towards more sophisticated, context-specific, and sustainable approaches.

Overarching Themes:

1. **Dengue as a Dynamic and Evolving Threat:** Dengue is no longer just a tropical disease; its vectors are expanding their geographical ranges due to climate change and globalization. The disease itself presents with diverse clinical manifestations, necessitating evolving diagnostic criteria.
2. **The Indispensable Role of Data:** Accurate, comprehensive, and real-time data collection and analysis are the bedrock of effective dengue management. Such data includes epidemiological data, entomological surveillance data, insecticide resistance profiles, and vaccine efficacy/safety data.
3. **Multi-Faceted and Integrated Control Strategies:** A "one-size-fits-all" approach is insufficient. Effective dengue control requires combining traditional methods (like source reduction and larviciding) with innovative technologies (e.g., *Wolbachia*, AI, drones) and robust public health interventions.
4. **Context-Specific Implementation:** The optimal strategy varies significantly by region, depending on factors like geographical size, resources, endemicity, predominant serotypes, and public acceptance.
5. **Importance of Public Engagement and Inter-sectoral Collaboration:** Sustained success in dengue control relies heavily on strong community involvement, public education, and seamless collaboration between various government agencies, research institutions, and healthcare providers.
6. **Addressing Insecticide Resistance and Environmental Concerns:** The widespread and often indiscriminate use of insecticides has led to resistance. Growing concerns about their environmental impact and human health risks (e.g., pyrethroids, PFAS) necessitate a shift towards more sustainable and safer alternatives.

Expert Recommendations:
Based on the detailed insights from all sessions, the following are key actions and strategies recommended by the experts:

1. Strengthen Government and Inter-sectoral Collaboration:

- Increase Public Health Capacity: Invest significantly in resources, infrastructure, and trained personnel to enhance the capacity to respond to and manage mosquito-borne diseases.
- Establish Economic and Public Health Research Agendas: Develop focused research plans to streamline efforts, foster coordination, and address specific economic and public health challenges related to dengue.
- Form Dedicated Dengue Teams: Emulate successful models where diverse government agencies (e.g., Health, Environment, Agriculture) collaborate to strengthen monitoring, leverage innovative technology, improve public health outcomes, and promote community involvement.
- Educate Stakeholders: Engage politicians to secure policy support and sustained funding. Educate the general public to counter misinformation, promote compliance with control measures, and build acceptance for new interventions.

2. Leverage Technology and Research for Enhanced Surveillance and Control:

- Embrace Advanced Technologies: Continuously integrate and expand the use of cutting-edge technologies, including:
  - AI-powered solutions: For smart traps, laboratory diagnostics (e.g., AI public lab detection), and automated pesticide application (UAVs/drones, UGVs, spray robots).
  - GIS and Modeling: Utilize tools like SITellite GIS and computer modeling for precise vector surveillance, risk mapping, and prediction of disease trends, even under high climate variability.
  - Molecular Diagnostics: Employ advanced molecular techniques (e.g., eDNA/RNA, pathogen detection, allele-specific qPCR, RPA-LFA) for rapid and accurate detection of mosquito-borne pathogens and insecticide resistance genes.
- Invest in Research & Development: Consistently fund and engage in research and development, collaborate with universities and companies to explore novel solutions like vector IDX, advanced diagnostics, biopesticides, and alternative control methods (e.g., *Wolbachia* strategy, Sterile Insect Technique - SIT, Attractive Targeted Sugar Baits - ATSB).
- Establish Data Repositories: Create urgent, unmet needs for an insecticide-resistant database repository in Asia. Centralized databases for resistance mechanisms (beyond the sharing between individual economies) are crucial for informed vector control strategies.

- Adapt to Climate Change: Increase resources and research on how global warming and globalization are creating new challenges for vector control, requiring adaptable and robust prediction models.

3. **Optimize Mosquito Control Strategies:**

- Multi-Modal and Integrated Approach: Implement a multi-faceted approach that combines:
    - Source Reduction: Reinforce the "NO WATER NO MOSQUITOES" principle and innovate container inspection methods, especially in environmentally complex areas.
    - Larviciding: Prioritize and extensively use larviciding, particularly with temephos, due to its continued effectiveness and relatively low resistance.
    - Targeted Chemical Control: Use adulticiding (chemical spraying) sparingly and only when absolutely necessary (e.g., during massive outbreaks). When used, coordinate carefully with other interventions like *Wolbachia* releases.
    - Strategic Use of Synergists: While most published studies focus on the molecular detection of kdr mutations, limited information is available on metabolic resistance. To address this gap, synergists that mainly consist of metabolic enzyme inhibitors targeting cytochrome P450 should be considered alongside pyrethroid insecticides.
    - Behavioral Resistance Monitoring: Develop and apply methods (like WHO and Kasetsart University assays) to detect and respond to behavioral resistance in mosquitoes.
- *Wolbachia* Implementation:
    - Contextual Selection: Choose between *Wolbachia* suppression (e.g., Singapore) and replacement (e.g., Indonesia; Malaysia) strategies based on the size of the area, available resources, and the overall objectives.
    - Community Buy-in: Prioritize extensive community engagement and consent as prerequisites for the implementation of a *Wolbachia* program, ensuring public understanding and cooperation (e.g., avoiding fogging in release areas).
    - Long-Term Monitoring: For replacement strategies, monitor human case reduction as the primary metric of success, acknowledging that mosquito population indices may remain constant. For suppression, evaluate mosquito reduction.
- Minimize Indoor Insecticide Use: Due to growing concerns about human health impacts (cardiovascular and neurological) and environmental persistence (PFAS, "forever chemicals") associated with pyrethroids, strongly advocate for minimizing indoor insecticide treatment and thermal fogging.

4. **Enhance Dengue Vaccine Development and Implementation:**

- Address ADE Challenges: Continue scientific efforts to understand and overcome Antibody-Dependent Enhancement (ADE), which remains a formidable challenge for dengue vaccines. Research into specific protein antigens causing ADE is crucial.
- Balanced Immune Response: Focus vaccine development on inducing equally balanced immune responses against all four dengue serotypes to minimize ADE risk.
- Rigorous Data Interpretation: Emphasize the rigorous interpretation of vaccine safety and efficacy data, particularly differentiating true adverse events from psychosomatic reactions (e.g., fainting attacks).
- Tailored Programmatic Considerations: Implement vaccine programs (like TAK-003) based on WHO recommendations, prioritizing high-transmission areas and specific age groups (e.g., school-going children and adolescents).
- Strategic Co-administration: Explore co-administration with other vaccines (HPV, Hepatitis A/B) to optimize coverage and reduce operational costs.
- Post-Marketing Surveillance: Conduct continuous, high-quality post-marketing surveillance to monitor vaccine effectiveness (especially against DENV3/DENV4), safety (including anaphylaxis), and specific outcomes in vulnerable populations (e.g., elderly, pregnant individuals).
- No Pre-vaccination Screening for Public Programs: Generally, pre-vaccination screening for serostatus is not advised for large-scale public health programs due to cost and logistical complexities. Nonetheless, travelers should be informed that the vaccine may provide limited protection against DENV3.
- Outbreak Response Limitations: Acknowledge that current dengue vaccines are generally not suitable for immediate outbreak response due to dosing schedules, delayed immune responses, and lack of supporting data. Further research is needed for this application.

5. **Enhance Public Engagement and Education:**

- Promote Community Involvement: Actively encourage and facilitate community participation in mosquito control efforts, from source reduction to supporting novel interventions.
- Counter Misinformation: Develop effective strategies to address public misinformation about mosquito control and new technologies by providing accurate, transparent information and showcasing the benefits.
- Utilize Educational Platforms: Leverage educational centers and museums for public outreach and long-term knowledge building.
- Constant Communication for New Programs: For new interventions like *Wolbachia* programs, ensure constant communication and reassurance to manage public expectations and maintain buy-in, especially when there might be initial increases in mosquito sightings.

Overall, the experts advocate for a holistic, adaptive, and scientifically grounded approach to dengue management. This approach integrates advanced surveillance, innovative control methods, safe and effective vaccines, and strong community partnerships, all driven by robust data and a deep understanding of local contexts to effectively combat the evolving threat of dengue globally.