

CONSENSUS OF VIETNAM PEDIATRIC ASSOCIATION DENGUE HEMORRHAGIC FEVER BURDEN AND PREVENTION RECOMMENDATIONS FOR CHILDREN IN VIETNAM

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INTRODUCTION

Dengue hemorrhagic fever (DHF) is an infectious disease caused by the dengue virus. There are 4 serotypes of the dengue virus: DENV-1, DENV-2, DENV-3 and DENV-4. The virus is transmitted from infected people to healthy people by mosquito bites. The *Aedes aegypti* mosquito is the main vector. In Vietnam, Dengue hemorrhagic fever is a year-round epidemic in many provinces and localities, causing a burden of disease and economic pressure on individuals, families and the health-social system.

Although Vietnam is doing very well in controlling the DHF epidemic with a prevention system and treatment regimen that has been regularly updated in each stage. However, it still requires sustainable prevention measures, which is also a challenge and urgent requirement today.

Based on this urgent need, the Vietnam Pediatric Association organized an expert workshop on the topic "Burden of Dengue Fever and Prevention Recommendations for Children in Vietnam" with the participation of Professors, Doctors, and Physicians who are leading experts in many fields such as Pediatrics, Infectious Diseases, Preventive Medicine. Through this workshop, the Vietnam Pediatric Association has developed a **"Consensus: Burden of Dengue**

Fever and Prevention Recommendations for Children in Vietnam".

The consensus content includes information in the reports of the reporters, reference documents, current policies, especially in-depth discussions by experts on the current situation of Dengue hemorrhagic fever in Vietnamese children. The consensus summarizes the epidemiological, clinical characteristics and current burden of Dengue hemorrhagic fever and updates effective preventive measures to help medical staff in the pediatric system to refer to and provide appropriate advice to people to effectively prevent Dengue hemorrhagic fever. The Vietnam Pediatric Association would like to express our sincere thanks to the experts, editorial board, and conference organizers who participated in and contributed to this consensus.

CONSENSUS CONTENT

Consensus 1: Dengue hemorrhagic fever is a burden that can cause death in both children and adults, affecting health, and affecting local health resources, the national economic and social foundation.

According to statistics from the World Health Organization, in the first 6 months of 2024 alone, more than 10 million cases and 6,508 deaths

were recorded due to dengue hemorrhagic fever globally. From April to June this year, Europe had up to 4,000 cases although before April there were no recorded cases of dengue hemorrhagic fever. In Vietnam, right after the COVID-19 pandemic, two consecutive years 2022 and 2023 witnessed a new peak of dengue fever with many changes in the nature of the epidemic cycle, the time between epidemic peaks shortened, and was difficult to predict. Many provinces and cities recorded a very high increase in the number of dengue hemorrhagic fever cases, even more than Ho Chi Minh City, the area with the highest dengue fever epidemic ever. Children, the elderly, people with re-infection, people with chronic underlying diseases, pregnant women (especially during labor), etc. are at risk of very severe disease progression and high mortality rate.

In general, dengue hemorrhagic fever is an urgent problem globally as well as in Vietnam. The number of DHF cases is increasing and there are still some unfortunate deaths, with economic burden and pressure on the treatment system, both in terms of infrastructure and medical human resources, especially in the pediatric treatment system.

Consensus 2: Dengue hemorrhagic fever tends to increase globally, as well as in Vietnam. The epidemiological characteristics of dengue hemorrhagic fever have appeared in all regions recently, the epidemic is difficult to determine the time. The average age of the disease tends to increase, shifting to the adult group, however, the group of children is still a large proportion. Children are infected at all ages, the average age of children is 2-4 years old.

The number of cases of dengue fever (DHF) is increasing and tends to be complicated, difficult to control in the world as well as in Vietnam. From 2024 to now, Brazil has recorded more than 6 million cases and 5,000 deaths due to dengue hemorrhagic fever. In Vietnam, in 2023, for the first time, Hanoi had twice as many cases of dengue hemorrhagic fever as Ho Chi Minh City. Recent developments (2024) also show that in the North, Hai Phong is also a hot spot with

more than 10,000 cases of dengue hemorrhagic fever, much higher than the number recorded in previous years. In the southern provinces, where the epidemic is circulating all year round, the number of recorded cases is very high. The nature of the dengue hemorrhagic epidemic cycle in Vietnam has changed due to many factors: the impact of climate change, urbanization, increasing average temperatures, increased domestic and international travel, etc.

Data on monitoring the epidemiological distribution by age shows that most of the dengue hemorrhagic fever in the North and Central Highlands is recorded in adults. In contrast, in the South, dengue fever is mainly found in children, this proportion is gradually changing (from 80% to about 40-50% of the total number of cases), however, the proportion of children is still large, mainly from the age groups of 5-14 and 25-44 years old. In fact, the burden of dengue hemorrhagic fever in children is still the main one.

Consensus 3: The Ministry of Health's guidelines for diagnosis and treatment of dengue hemorrhagic fever have been issued and updated regularly. The epidemic prevention work has been well implemented, and coordination between departments and branches from central to local levels has significantly reduced the mortality rate due to DHF.

Based on 3 versions of the treatment guidelines of the World Health Organization (WHO), the Guidelines for Diagnosis and Treatment of Dengue Hemorrhagic Fever have been issued and updated by the Vietnam Ministry of Health in each period in a timely manner (2004, 2011, 2019, the latest is 2023). The recorded mortality rate in Vietnam is very low (0.02% - 0.03%), however, the effort to save just one severe case requires a lot of effort, not to mention the burden of high treatment costs (severe cases can cost up to VND 120 million - 720 million/case). In addition, our country's treatment system still faces many challenges from unsafe hospital transfers, difficult detection and treatment of brain complications with high mortality rates,

pressure on overloading many treatment facilities, etc. Therefore, it is recommended to increase online consultations combined with training and coaching to improve the capacity of the treatment system from central to local levels.

Preventive measures being implemented by the preventive health system nationwide include two main groups of solutions:

Environmental management measures: The purpose of this measure is to eliminate favorable environments for mosquitoes to lay eggs. This is a comprehensive measure including long-term measures such as improving the domestic water supply system and short-term measures such as regularly removing artificial and natural water containers or waste materials in households and communities.

Controlling disease vectors (killing mosquitoes, larvae, pupae, etc.): The goal of this measure is to prevent and eliminate the "Aedes - human" link in the disease cycle. It includes many different methods: (1) Mechanical measures: using curtains, blinds, screen doors, etc. to prevent mosquito bites; using high-frequency waves to repel and kill mosquitoes; using mosquito traps, mosquito swatters, etc. are widely used at the individual, family and community levels. (2) Chemical measures: use chemicals to kill mosquitoes, use chemicals to kill mosquito larvae by releasing chemicals into water (not into domestic water) to limit the ability to develop/kill mosquito larvae, etc. (3) Biological measures: use natural enemies of mosquitoes and mosquito larvae (guppies, sailfish, perch, Mesocyclops, etc.) released into jars/vats/water tanks to eat mosquito larvae (wiggler); use genetic technology to create populations of genetically modified mosquitoes, use Wolbachia bacteria, etc. Some projects related to the use of Wolbachia in the world as well as in Vietnam have shown effectiveness in reducing new cases of DHF.

Although Vietnam is doing very well in controlling DHF with a prevention system and treatment regimen that has been regularly updated in each stage; however, it still requires

sustainable prevention measures, which is also a challenge and urgent requirement today.

Consensus 4: In addition to traditional DHF prevention measures that have been well implemented in the past, there should be a coordinated prevention of the disease using vaccines. This coordination is a valuable overall solution, effectively reducing cases of dengue hemorrhagic fever and deaths, helping to reduce the burden on national resources.

Current DHF prevention measures are still non-specific measures such as vector control, consuming a lot of resources and costs; however, the effectiveness is not as high as expected. Therefore, the solution of using vaccines is still a specific and optimal preventive measure.

DHF vaccine solution: There are currently two vaccines that have passed the clinical trial stage and are licensed for use, CYD-TDV (Sanofi) and TAK-003 (Takeda), which have differences in vaccine "skeleton" design as well as indications for use. *Among them, TAK-003 vaccine has some advantages: indicated for use from 4 years of age and older, no need to test to confirm previous dengue infection, TAK-003's protective effect is maintained for 4 to 5 years even though it decreases over time.*

The requirements for an optimal DHF vaccine include: (1) Achieving a balance between efficacy and safety through a balance of reduced virulence; (2) Achieving a balance of immune response against all 4 dengue virus serotypes; (3) Having safety and long-term protective effect regardless of previous exposure to DHF; (4) Being able to respond and apply to diverse epidemiological situations in many parts of the world; (5) Meeting the needs for large-scale vaccination programs.

Currently, 40 countries have approved and licensed the use of the TAK-003 vaccine (countries in the European Union (EU), Thailand, Malaysia, etc. Some countries have included this vaccine in the expanded and widespread immunization program such as Brazil, Argentina and Indonesia.

Vietnam is the 37th country to approve the TAK-003 vaccine (Qdenga), the Ministry of

Health licensed it on May 14, 2024. DOI: <https://dichvucong.dav.gov.vn/congbothuoc>

Consensus 5: The protective efficacy and safety of the TAK-003 vaccine on children (4-16 years old) have been proven by research with sample sizes and standards required by the World Health Organization. Vietnam has also licensed and indicated the vaccine for people aged 4 years and older.

Regarding the clinical data of the TAK-003 vaccine: TAK-003 has many advantages and overcome the shortcomings of previous vaccines. Comprehensive research program on TAK-003 vaccine, DEN-301 Study on more than 20,000 participants aged 4-16 years, in 8 countries in dengue endemic areas.

With the following results on efficacy and safety: **(1) Regarding efficacy (VE):** TAK-003 achieved 80.2%¹ prevention of virologically confirmed DHF (VCD) after 12 months; achieved 90.4%² prevention of hospitalization due to VCD after 18 months from the completion of 2 injections. **(2) Long-term follow-up data after 54 months** (4.5 years) showed that TAK-003 efficacy maintained at 61.2% prevention of VCD and 84.1% prevention of hospitalization due to VCD. **(3) Regarding safety data**, there was no difference between the TAK-003 group and the placebo group in terms of both actively and non-actively collected adverse events (AEs), serious adverse events (SAEs). In addition, TAK-003 has been prequalified by WHO (May 9, 2024) as a quality, safe and effective vaccine. **(4) TAK-003**, there is no need to screen for previous exposure to DHF.

Analysis of safety data in clinical trials, there was no difference between the 2 vaccine groups and the placebo group in terms of both actively and non-actively collected adverse events (AEs), serious adverse events (SAEs). However, although

not recorded in clinical studies, in practice, vaccination in some countries has shown that there have been some cases of anaphylactic reactions in Brazil (equivalent to 4.4/100,000 doses) according to the announcement of the World Health Organization (WHO) in May 2024. This suggests that data on vaccine safety need to be regularly updated, followed up and monitored for adverse reactions after vaccination, especially serious adverse events from both actual vaccination data in countries around the world.

Information from experts on safety issues, current data shows no cause for concern, although the rate of anaphylactic shock recorded after vaccination in Brazil, however, all cases were treated on the spot, without the need to go to the hospital. World experts all believe that the benefits are much greater than the risks and national vaccination programs in many countries continue to be carried out.

Consensus 6: The Vietnam Pediatric Association agrees to recommend active prophylaxis with the DHF vaccine (TAK-003, Qdenga) for people aged 4 years and older, without testing to assess previous exposure status and following the instructions in the manufacturer's prescribing information licensed by the Ministry of Health on May 14, 2024.

Study data on subjects aged 4-16 years are sufficient, except for data on efficacy in subjects who have never been infected with DHF on DENV-3 and DENV-4 types, which are lacking due to the small sample size, and are not conclusive. However, WHO recommends that serological screening tests are not required before TAK-003 vaccination.

According to the World Health Organization (WHO)'s view on national immunization programs, the optimal age to consider for national immunization is 1-2 years before the peak age of hospitalization, with priority given to 6-16 years. However, epidemiological data and peak age of hospitalization in each country and region such as the North and the South will be different, and further consideration should be given to serological databases to determine the optimal

¹ 80.2% vaccine efficacy against infection: Vaccination reduces the risk of infection by 80.2% in vaccinated people compared to unvaccinated people.

² 90.4% efficacy against hospitalization: Vaccination reduced the risk of hospitalization by 90.4% in vaccinated people compared with unvaccinated people.

age if included in the expanded immunization program in Vietnam.

Regarding recommendations for countries with difficult economies, priority should be given to prevention because the cost of treatment is very expensive. A health-economic study in Thailand showed that the model of evaluating annual TAK-003 vaccination for 11-year-old children after 20 years has a positive impact, achieving high cost-effectiveness: estimated to reduce 34% of cases, 30% of asymptomatic cases, 41% of symptomatic cases, 50% of hospitalizations and 50% of deaths due to dengue fever; in terms of health-economics, TAK-003 vaccine helps reduce 155,407 DALYs (disease-adjusted life years (years of life lost due to disease)), helping society save USD 1.37 billion from direct and indirect medical costs, lost income, lost school days as well as the vaccine helps payers save USD 744 million from reduced direct medical costs.

Consensus 7: The Vietnam Pediatric Association emphasized the need to continue to update and supplement data on the efficacy, effectiveness and safety of the TAK-003 and Qdenga vaccines. Special attention should be paid to monitoring and supervising serious adverse events after vaccination from all countries in the world to promptly update and make appropriate recommendations.

Infectious disease and pediatric experts all affirm that the vaccine solution is the most important solution in preventive medicine, especially for Dengue hemorrhagic fever, early access to vaccines should be provided when possible.

For most vaccines, small-scale vaccination should be implemented before being included in the expanded immunization program, considering both post-vaccination safety and drawing experience for larger-scale implementation. With dengue fever vaccines, it is also necessary to prepare full instructions on safe vaccination practices, Q&A documents on vaccine use, from which health workers have information to fully advise parents because the vaccination target is children. Although

data on vaccine safety have been recorded in a number of studies and the vaccine has been used in a number of countries, the vaccine has been licensed for circulation by the Drug Administration, monitoring post-vaccination reactions needs to be focused on, promptly handled to deploy new vaccines to ensure safety, avoiding risks that affect vaccine coverage.

Experts agree that it is necessary to closely monitor and report adverse events after vaccination, especially serious events such as anaphylaxis. The important issue is the need to regularly update vaccine safety data and pay attention to communication and education issues when deploying vaccination.

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