FINDINGS OF THE 14 DEATHS WITH PRIOR DENGVAXIA® VACCINATION BY THE DOH-COMMISSIONED INDEPENDENT EVALUATION TEAM OF PHYSICIANS, THE PHILIPPINE GENERAL HOSPITAL DENGUE INVESTIGATIVE TASK FORCE (PGH DITF): AN INTERIM REPORT

EXECUTIVE SUMMARY

Under the directives of the Department of Health (DOH) Sec. Francisco T. Duque and the Philippine General Hospital (PGH) Director Dr. Gerardo D. Legaspi, the PGH Dengue Investigative Task Force (PGH DITF) was organized by Dr. Juliet O. Sio-Aguilar, Chair of the Department of Pediatrics, to serve as the independent body of expert physicians of PGH to evaluate the deaths of 14 children who were given one to three doses of the Dengvaxia® vaccine.

The DITF was instructed to thoroughly review each case to address the growing concern of the general public regarding the safety of the Dengvaxia® vaccine. The DITF was specifically tasked to determine the cause of death of each child and to assess if any possible association existed between the death and the vaccination.

The selection of members of the DITF was based on the following qualifications: the physician (1) must not be affiliated with any vaccine company, and (2) must not have administered the dengue vaccine to any patient. As a result of the stringent process of selection, the DITF formed consisted of 10 members: two (2) pediatric cardiologists, two (2) pediatric infectious disease specialists, one (1) pediatric emergency specialist, one (1) allergist/immunologist, one (1) pediatric gastroenterologist, one (1) pediatric nephrologist, one (1) neonatologist, and one (1) forensic pathologist. This 10-person team was complemented by four (4) other subspecialists whose expert opinions were solicited to clarify certain cases; these specialists were a pediatric neurologist, a pediatric hematologist-oncologist, a geneticist, and a rheumatologist. A team of three (3) pediatric residents served as the DITF's secretariat.

In undertaking its task, the DITF identified the following terms of reference: **definition of terms, mechanics and tools of evaluation, and process flow**. The DITF then adapted the World Health Organization (WHO) Algorithm for Causality Assessment of Adverse Events Following Immunization (AEFI) as its evaluation tool.

The WHO Algorithm for Causality Assessment of AEFI[1] is a systematic, scientifically sound, and universally accepted process of assessing causality of events following any vaccination. Based on this tool, the outcomes may be categorized as follows:

A. Consistent with causal association to immunization
   A1. Vaccine product-related
   A2. Vaccine quality defect-related
   A3. Immunization error-related
   A4. Immunization anxiety-related
B. Indeterminate
   B1. Consistent temporal relationship but insufficient evidence for vaccine causing the event
   B2. Conflicting trends of consistency with causal association to immunization
C. Inconsistent with causal association to immunization (coincidental)
   Presence of underlying or emerging condition; or other condition caused by exposure to something other than the vaccine
D. Unclassifiable (additional information to determine causality is needed)

[1] IMPORTANT: Please refer to the accompanying FACT SHEET ON AEFI and Causality Assessment for clarification of definitions.

Of the fourteen (14) cases evaluated, the results of the DITF's evaluation are as follows:

- Three (3) cases under Category A1: consistent with causal association to immunization that is vaccine product-related; two (2) of which implicated vaccine failure;
- Six (6) cases under Category B1: indeterminate only because of the consistent temporal relationship within a month of exposure of the vaccine but insufficient evidence for the vaccine causing the event;
- Three (3) cases under Category C: coincidental because there was inconsistent causal association to immunization; and
- Two (2) cases under Category D: unclassifiable due to inadequate information available.

The DITF recommends further investigations in order to clarify the nature of the association with vaccination or the cause of death for the following cases:

- All three (3) A1 cases (Cases 1, 2, and 3) and two (2) indeterminate B1 cases (Cases 5 and 6) are recommended for further tissue evaluation for polymerase chain reaction (PCR) RNA of dengue virus, viral sequencing, and antibodies for the yellow fever and dengue viruses. Yellow fever-related tests are recommended as Dengvaxia® is a live attenuated vaccine using recombinant DNA technology created on the yellow fever (YF 17D) backbone.
- One (1) indeterminate B1 case (Case 9), one (1) coincidental case (case 13), and both unclassifiable cases (Cases 12 and 14) may be subjected to further investigations, such as an autopsy to determine the nature of their disease and the cause of death.

The results of this evaluation are to be forwarded to the Pharmacovigilance Team of the DOH for further investigation and/or signal detection for possible new causal association. Only then can the investigation of these cases be completed and the results considered final.

Overarching the DITF recommendations is the call to ensure that:

- clear, specific, and appropriate information be given to the public on dengue infection – its clinical presentation, actions to be taken for suspect cases, and preventive measures; and
- all health practitioners do a thorough review of the existing treatment guidelines, particularly fluid management, in the care of such patients.

FACT SHEET:
ADVERSE EVENT FOLLOWING IMMUNIZATION (AEFI) AND CAUSALITY ASSESSMENT

IS THERE A SYSTEM OR PROCESS FOR CHECKING WHETHER AN INCIDENT OR OUTCOME IS RELATED TO VACCINATION LIKE DENGVAXIA®?

Yes, the World Health Organization has developed a systematic, standardized, global process for evaluating whether an incident or outcome is related to any vaccination. This is the WHO Causality Assessment of Adverse Event Following Immunization (AEFI).

WHY WAS THE CAUSALITY ASSESSMENT FOR AEFI ESTABLISHED?

Immunization safety is an important aspect of vaccine development, just as the effectiveness of a vaccine is crucial. Unlike medicines or drugs, the expectations from vaccines (and vaccination) are much higher because these are given to healthy people. The reality is that the benefits of immunization are often not as obvious or visible and that it may even take months to years before an impact to the person and/or the society can be known. Thus, allegations that vaccines or the vaccination process cause adverse events must be addressed because this issue may have negatively influence immunization coverage.

It is thus the purpose of the WHO to guide the healthcare system to objectively analyze the events that occur surrounding the vaccination.

WHAT DO YOU MEAN BY CAUSALITY?

Causality is simply the relationship between two events, where the second event is a consequence of the first. A direct cause is a factor in absence of which the effect would not occur (necessary cause). Sometimes, there are multiple factors that may precipitate the effect (event) or may function as co-factors so that the event occurs.

WHAT IS CAUSALITY ASSESSMENT?

Causality assessment usually will not prove or disprove an association between an event and the immunization. It is intended to assist in determining the level of certainty of such an association. A definite causal association or absence of association often cannot be established for an individual event.

WHAT IS AN ADVERSE EVENT FOLLOWING IMMUNIZATION (AEFI)?

This refers to any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the use of the vaccine. The adverse event may be any unfavorable or unintended sign, an abnormal laboratory finding, a symptom or a disease.

WHAT IS VACCINE FAILURE?

Vaccine failure refers to the development of the specific disease being prevented by the vaccine in a person who is appropriately and fully vaccinated, taking into account the incubation period of the disease and the normal delay for the protection to be acquired as a result of immunization. This may refer to both the vaccinee (or host)-related and vaccine-related factors.

WHAT IS VACCINE PHARMACOVIGILANCE?

This involves the science and activities relating to the detection, assessment, understanding, and communication of adverse events following vaccine- or immunization-related issues, and relating to the prevention of untoward effects of the vaccine or immunization. The goal is early detection of and the appropriate and timely response to AEFIs in order to minimize negative effects to the health of individuals and lessen the potential negative impact on immunization of the population.

WHAT IS A SAFETY SIGNAL?

A signal is an information (from one or multiple sources) which suggests a new and potentially causal association, or a new aspect of a known association between an intervention and an event, or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.

WHY IS VACCINE PHARMACOVIGILANCE IMPORTANT?

There is a very high level of safety required for vaccines. The elements to consider when conducting vaccine pharmacovigilance include the following:

- Vaccines are usually administered to healthy people, including infants.
- Vaccines may be administered to the vast majority of the population or of a birth cohort or to groups at high risk for disease complication.
- The age at the time of immunization may coincide with the emergence of certain age-related diseases.
- Immunization with certain vaccines is mandated in some countries.
- The benefits of immunization may not be immediately visible, particularly if the target disease incidence is low.
- Consideration of dechallenge and rechallenge differs for vaccines compared with other medicinal products. Vaccines are frequently administered only once or with long intervals, and serious AEFIs often prevent further vaccine administration. Dechallenge may not be possible with vaccines, given their long- term immunological effects.
- The administration of live vaccines can lead to disease caused by the attenuated organisms in vaccines or their contacts; this should be differentiated from coinciding natural infection.
- Vaccines are complex biological products, which may include multiple antigens, live organisms, adjuvants, and preservatives. Each component may have unique safety implications. Variability and (even small) changes in the manufacturing process may have impact on quality, protective effect, and safety. Batch information is of crucial importance.
- The need for vaccines is increasingly based on new production and administration technologies, with new adjuvants and alternative routes of administration, necessitating adapted safety monitoring systems.
- Effective communication regarding the safety of vaccines and immunization is challenging. Despite strong evidence that a serious adverse event is not related to immunization, perceptions of harm may persist and may potentially have a negative impact on immunization of the population.

References:

Fosberg, et al., Definition and Application of Terms for Vaccine Pharmacovigilance (Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). WHO. 2012.

WHO. Causality Assessment of an AEFI: User Manual for the Revised WHO Classification. 2013.