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**FINAL STATEMENT BY THE PAN AMERICAN HEALTH ORGANIZATION/WORLD HEALTH ORGANIZATION (PAHO/WHO) ON**

**INVESTIGATION OF SERIOUS ADVERSE EVENTS IN PERU FOLLOWING RECEIPT OF YELLOW FEVER VACCINE PRODUCED BY BIO-MANGUINHOS, BRAZIL**

**Date issued: 21 March 2008**

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This PAHO/WHO statement provides results of the investigation of serious adverse events that occurred in October 2007 following administration of yellow fever vaccine (17DD sub-strain) manufactured by Bio-Manguinhos, Brazil.

A previous PAHO/WHO statement on the reported events was issued on 2 November 2007 and recommended temporary suspension of specific lots of the vaccine.<sup>1</sup>

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***Background***

From November 2007 to March 2008, the Pan American Health Organization and the World Health Organization (PAHO/WHO) assisted the Ministry of Health in Peru to investigate serious adverse events, including four deaths, which occurred during a yellow fever vaccination campaign from 23 September to 6 October 2007 in the Ica Region, south of Lima. The four fatal cases occurred in persons ranging in age from 23 to 79 years who had received a single lot of vaccine (05OVFA121Z), among an estimated 42,742 persons vaccinated with the specified lot. An additional 20,432 people were vaccinated in Ica with a different lot (05OVFA123Z); however, no deaths were reported in this group.

A PAHO/WHO statement was issued on 2 November 2007 to alert the global public health community to the occurrence of these cases and outlined the planned investigation to determine the potential causal relationship with yellow fever vaccine. The cases constituted the first report of multiple cases of viscerotropic disease linked to the use of a single vaccine lot. Pending the results of the investigation, PAHO/WHO recommended a temporary suspension of the implicated lot and related lots<sup>1</sup> of the Bio-Manguinhos yellow fever vaccine. The subsequent investigation, including epidemiological, virological, molecular and pathological analyses of cases as well as vaccine testing, was further supported by the US Centers for Disease Control and Prevention (CDC) and an Expert Panel convened to assist the investigation.

Acute viscerotropic disease following yellow fever vaccination is a rarely reported but life-threatening adverse reaction first recognized in 2001. Up to September 2007, 36 probable or confirmed cases of viscerotropic disease had been reported globally following vaccination with both 17DD and 17D-204 substrain yellow fever vaccines. It most typically presents as a yellow fever-like illness with multiple organ failure, and an average onset of symptoms 2-5 days following receipt of yellow fever vaccines. The estimated risk for viscerotropic disease following yellow fever vaccination is approximately 0.3-0.4 per 100,000 vaccinated persons overall; a higher risk has been documented in persons older than 60 years and in other selected settings/subpopulations.

***Findings of the case investigation***

Epidemiological and virological investigations of the reported adverse events were conducted. Data from the routine adverse event surveillance system in Peru and retrospective case-finding

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<sup>1</sup> Lot 05OVFA121Z and related lots in production, specifically 05OVFA118Z, 05OVFA119Z, 05OVFA120Z, 05OVFA122Z, 05OVFA123Z, 05OVFA124Z, 05OVFA125Z, 05OVFA126Z.

detected a total of 11 cases of serious adverse events (all 11 cases were detected by routine surveillance and no additional serious adverse events were detected by retrospective case-finding). They included the four fatal cases (associated with a single lot 05OVFA121Z of Bio-Manguinhos yellow fever vaccine) and one surviving case all of whom presented as suspected viscerotropic disease and were reported in the Ica Region. The other five cases occurred in other regions. The vaccine lot used in the fifth non-fatal case is currently unconfirmed. One additional (non-fatal) reported adverse event from the Ica Region was determined to be unrelated to vaccination.

The five suspected cases of viscerotropic disease presented with a similar clinical picture of fever, headache, malaise, myalgia, and diarrhea in some, progressing rapidly to distributive shock and irreversible multiple organ failure. The onset of symptoms ranged from less than 24 hours to one week after vaccination in four cases (the onset interval in the fifth case was unclear).

The laboratory diagnosis of these five cases revealed a wide tissue distribution of vaccine virus (affecting many vital organs), high viremia, and a high virus load, and high antibody titers consistent with previous reported cases of viscerotropic disease. The genomic sequences of viral RNA from three fatal cases were determined to be consistent with vaccine virus from lot 05OVFA121Z. Importantly, there was no evidence of a change in the vaccine virus (a mutation or selection of a variant) that could explain these cases.

Five other cases of serious adverse events were identified from other regions (none had received lot 05OVFA121Z and each had received a different lot of yellow fever vaccine), including one death in a 20-month old infant. This fatal case was investigated virologically with no laboratory evidence of infection by vaccine virus and the cause of death was determined to be hemolytic anemia.

The search for additional cases, as noted above, was based on retrospective review of over 27,000 records of hospitalizations, emergency visits and deaths in five provinces in the Ica Region, and yielded no additional serious adverse events. The adverse event surveillance system was thus determined to be highly sensitive.

### ***Vaccine quality review***

The yellow fever vaccine produced by Bio-Manguinhos is prequalified by WHO since October 2001 and supplied through the PAHO Revolving Fund and UNICEF to several countries for routine immunization, preventive and outbreak control campaigns, and for immunization of travelers.

A vaccine quality review was carried out by a team comprising PAHO/WHO experts and independent experts, and included a review of batch manufacturing records, GMP, and other manufacturing and quality control processes.

The vaccine quality review showed that lot 05OVFA121Z and related lots produced from the same viral suspension were in compliance with WHO quality standards for production of yellow fever vaccine. No evidence of quality problems or deviations during the production process was found with the specific lots of the Bio-Manguinhos yellow fever vaccine, or with the vaccine in general to explain the adverse events

### ***Conclusions of the Expert Panel***

The incidence of yellow fever vaccine-associated viscerotropic disease in Ica Region in this event is significantly higher (more than 20 times) than observed previously in other settings. Five cases occurred among 63,174 vaccinated persons for an overall rate of 7.9 per 100,000. Previous estimates of the overall incidence are approximately 0.3-0.4 per 100,000 vaccinated persons. A number of hypotheses were considered to explain the higher rate, and eliminated, including the possibility that the vaccine lot 05OVFA121Z contained a genetic change responsible for enhanced virulence and possible host factors that may have contributed to susceptibility in the cases.

The investigation showed clinical, virological and pathological evidence of confirmed viscerotropic disease in 4 fatal cases and probable viscerotropic disease in 1 surviving case. The cause of death was an overwhelming infection with 17DD vaccine virus, probably associated with a severe immune response syndrome.

Multiple lines of investigation indicated that there were no changes in the vaccine virus that were responsible for the occurrence of these cases. No evidence could be found to suggest that the vaccine lot 05OVFA121Z had anything inherently wrong with it to explain the higher frequency of viscerotropic disease in persons receiving that lot.

All fatal cases had some underlying or concurrent condition that might have contributed to the fatal outcome of the adverse events. The fact that other, non-identified risk factors may have contributed to the increased rate of viscerotropic disease in this Region is not rule out.

### ***PAHO/WHO recommendations***

All lots affected by the PAHO/WHO temporary suspension issued last year<sup>1</sup> expired before or by 31 December 2007. It is emphasized that all lots were in compliance with the quality standards. Nevertheless, on the basis of the expiry of those lots, PAHO/WHO strongly recommends that, in countries where stocks remain on hold, all remaining stocks of the specified lots that were put under temporary suspension be discarded.

Vaccination with the live, attenuated 17D vaccine remains the most effective measure for yellow fever prevention and control. PAHO/WHO re-emphasizes the current recommendations for vaccination, particularly contraindications and precautions against vaccination, including assessments of special groups with potential risk for serious adverse events when appropriate, as detailed in the current WHO Position Paper on yellow fever vaccine<sup>2</sup> and report of the Global Advisory Committee on Vaccine Safety meeting held 2-3 December 2004.<sup>3</sup>

Health workers should take care to ensure that careful consideration is given to the risks and benefits of vaccination in all situations and that only persons who are truly at risk of exposure to yellow fever are vaccinated. Such risk-benefit assessments to decide on indications for vaccination need to be appropriately considered both in the context of mass vaccination campaigns and for potential vaccination of individuals (e.g., for travel by at-risk persons to high-risk areas or for individuals at risk for occupational exposure to yellow fever infection).

PAHO/WHO further recommends that all countries using yellow fever vaccine enhance their capacity to detect and appropriately investigate serious adverse events following immunization.

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<sup>2</sup> Weekly Epidemiological Record, No 40, 2003, pp 349-359

<sup>3</sup> Weekly Epidemiological Record, No 1, 2005, pp 3-7