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Yellow Fever Vaccine Post-marketing Surveillance in Brazil

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Abstract

Viscerotropic disease (VD), a disease with high mortality, results from the dissemination of the yellow fever vaccine virus throughout the body. Twenty-six cases of VD following vaccination with the Bio-Manguinhos 17DD vaccine were reported, 21 from Brazil and 5 from other countries, of which 19 were confirmed, 4 probable and 3 suspect. These cases were not related to immunodeficiency diseases, but could be related to the existence of autoimmune diseases, such as systemic lupus erythematosus. Adverse neurological events following yellow fever vaccination are in general aseptic meningitis, with a good outcome, encephalitis, and autoimmune neurological events such as Guillain-Barré syndrome. In Rio Grande do Sul (2009) 2 cases of confirmed meningoencephalitis in newborns after yellow fever vaccination of a breastfeeding mother created a new and difficult problem to solve in a satisfactory manner. Bio-Manguinhos/Fiocruz is doing several studies to try to improve the yellow fever vaccine, such as a dose-response study, with the objective to know if the vaccine can be administered in a smaller dose than usual, which perhaps would be safer, Also, further purification of the current vaccine, and studies for the development of a non-live yellow fever vaccine are under way.

Keywords: *Yellow fever vaccine; serious adverse events; post-marketing surveillance; viscerotropic disease; neurotropic disease.*

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1. Introduction

Yellow fever (YF) is in expansion in Brazil, with an eastward trend, menacing the highly populated coastal area. People from endemic areas or travelers to these areas are vaccinated. The yellow fever vaccine (YFV), a live attenuated virus strain (17DD) has been extensively studied, through molecular characterization, animal studies and clinical studies [1, 2, 3], and has shown genetic stability through repeated passages [4].The incidence of common adverse events, such as pain, myalgia and fever is at a low 4% of vaccinated people [5]. In the last 10 years, however, serious and even fatal adverse events have been reported after YFV administration. These are YFV-associated viscerotropic disease (VD), due to dissemination of the vaccine virus to viscera, YFV-associated neurological disease (ND), which includes benign aseptic meningitis, encephalitis, and autoimmune central or peripheral disease (Guillain-Barré Syndrome, GBS), as well as hypersensitivity events or anaphylactic shock.

The most serious adverse event is VD, which is characterized by a very high lethality. In Brazil, VD has been detected mostly after large vaccination campaigns in 1999-2001 and again in 2008-2009. Molecular studies of the virus isolated from these cases failed to find any significant mutation or contamination problems [6, 7].

Herein we present a summary of some post-marketing surveillance findings regarding serious adverse events after YF vaccination.

1. Methods

Since 1998, the National Immunizations Program at the Ministry of Health (MoH) established a National System for Surveillance of Adverse Events Following Immunization (AEFI), a manual on AEFI was conceived and adopted, which is now in its second edition, and an electronic database was implemented. The source of information is the 30,000 Health Centers all over the country, with evaluation of events at state level and final classification at national level. There are electronic adverse events databases at state and federal levels, and the information is shared with the Bio-Manguinhos Pharmacovigilance Unit. The Customer Service and Marketing Division in Bio-Manguinhos / Fiocruz also receives complaints from customers, and a Pharmacovigilance Unit has been established, connected to the MoH and the Brazilian Regulatory Authority (Anvisa).

A manual on AEFI for intermediate level health professionals has also been written and distributed, so, by now, there is a general understanding in the country that, although vaccines are the best health intervention, they are not perfect, and their use must follow a risk-benefit analysis. Recently, we have used the World Health Organization Manual for Detection of Serious Adverse Events after YFV. Cases were classified according to the Centers for Disease Control and Prevention (CDC) criteria, with minor adaptations. Detection and diagnosis was done at local level, with consolidation of diagnosis at the state level and final diagnosis at central level, with the participation of experts. A network of state laboratories and reference laboratories at national level provide good support for differential diagnosis and confirmation of VD or ND, with capability to carry yellow fever virus isolation in cell cultures, RT-PCR, immunohistochemistry, histopathology, and specific serology.

A Guideline for Investigation of Serious Adverse Events has also been developed and distributed, as well as a simple flow chart, explaining how to collect, transport and deliver samples from patients to laboratories. A special box for the collection of samples is sent to hospitals at the time of yellow fever vaccination campaigns. This is a one-contact sample procedure, useful for field work in difficult conditions.

Another important source of information is sentinel hospitals in charge of the detection of icterohemorrhagic febrile syndrome. This is a compulsory and immediate reporting. Differential diagnosis in Brazil includes wild yellow fever, VD, dengue, hantavirus, leptospirosis, meningococcal infection, malaria (*Plasmodium falciparum*), rickettsial infections, typhoid fever, Brazilian purpura fever and other arbovirus infections.

International organizations also provided information on cases outside Brazil.