

The Safety of Yellow Fever Vaccines, International Experience for Different Cases

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Abstract

Yellow fever virus is from family flaviviridae and is endemic in African countries and Latin America. Over 900 million people are living in endemic area and are risked from infection of yellow fever. Illness ranges in severity from a self-limited febrile illness to severe liver disease with bleeding and is diagnosed based on symptoms, physical findings, and laboratory testing and travel history, including the possibility of exposure to infected mosquitoes. There is no specific treatment for yellow fever; care is based on symptoms. The steps necessary to prevent yellow fever virus infection include using insect repellent, wearing protective clothing and getting vaccinated. Yellow fever vaccine is recommended for endemic countries and over 500 million people are vaccinated with yellow fever vaccine 17D. The countries which are not endemic are recommended according to International Health Regulation to vaccinate people in cases of travelling in endemic areas to avoid the importation of yellow fever virus and epidemic outbreak in the country. The cases of yellow fever infection are reported and in countries free of yellow fever virus. According the data based on the different studies in different countries the yellow fever 17D and 17DD vaccines are very safe and effective against illness and the best way for preventing yellow fever infection.

Keywords: Yellow fever virus; Vaccine; Adverse event following immunization

Introduction

Yellow Fever Virus (YFV) is a ribonucleic acid belong the genus flavivirus, antigenically related to West Nile Virus (WNV), St. Louis Encephalitis Virus and Japanese Encephalitis Virus. The virus of yellow fever found in tropical and subtropical countries in South Africa and South America and the virus transmitted through the bite of an infected *Aedes* or *Haemagogus* species mosquito. The transmission of the virus can happened from monkey to human or human to human via these mosquitoes. Human infected with YFV experience the highest level of viremia and are infectious to mosquitoes shortly before the onset of fever and for 3-5 days thereafter. The highest levels of viremia attained in humans occur through the transfusions of blood donated from donors recently immunized with vaccine against yellow fever. The transmission of the YFV can occur an urban cycle (in which transmission is carried from human to human by domestic mosquitoes). The virus is maintained in nature by a jungle transmission cycle involving monkeys as the reservoir, and tree-hole breeding mosquitoes as the vector. When humans come into contact with the jungle vector, they are at risk for infection (jungle transmission cycle) [1]. Other mosquitoes such as the tiger mosquito can serve as a vector. Illness ranges in severity from a self-limited febrile illness to severe liver disease with bleeding and is diagnosed based on symptoms, physical findings, laboratory testing and travel history, including the possibility of exposure to infected mosquitoes. There is no specific treatment for yellow fever; care is based on symptoms. Steps to prevent yellow fever virus infection include using insect repellent, wearing protective clothing, and getting vaccinated. The YFV infection disease was known more than 400 years ago and cause viscerotropic and neurotropic infection. Viscerotropic infection cause: temporary viraemia, hemorrhage, impairment in liver, spleen, kidney and heart and bleeding. Neurotropic infection infects the functional part of the brain and cause encephalitis. The infection occurs in nature in rodent of tangle and "outdoor" and wild type viruses do not cause the neurotropic disease in nature [2].

The Spreading of Yellow Fever Virus

Why exist the risk in EU/EEC? In European Union/ European

Countries YFV is risk of transmission only from people that are not vaccinated and travel in endemic area of the virus. The presence of *Aedes aegypti* mosquitoes as the primary vector of YFV in urban settings (Madeira, Portugal), is another reason of YFV risk. Also the European citizens who travel or live in endemic countries of YFV can be the source of transmission of the virus. In this case is important to explain those people the risk of infection from virus and if they are not vaccinated, need vaccination, recommendation to prevent the bite of mosquitoes especially early in the morning and during the sunset.

The Figure 1 shows the areas with risk of yellow fever virus transmission in Southern Africa and South America. Countries/areas where "a risk of yellow fever transmission is present," as defined by the World Health Organization, are countries or areas where "yellow fever has been reported currently or in the past, plus vectors and animal reservoirs currently exist" [2]. These countries are not holoendemic (only a portion of the country has risk of yellow fever transmission).

The Situation of Spreading of YFV in Year 2016

Angola

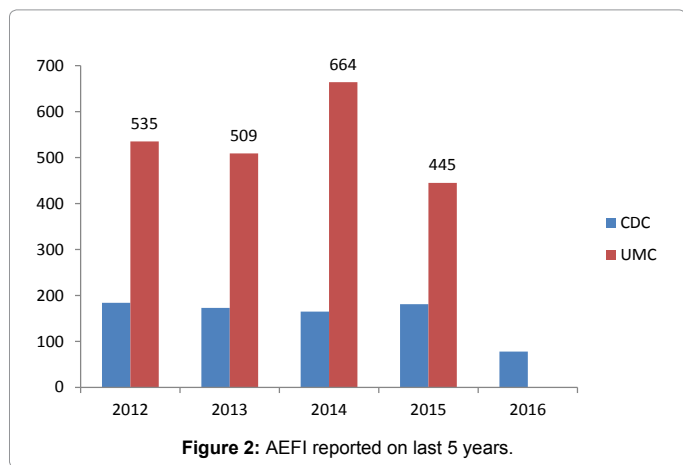
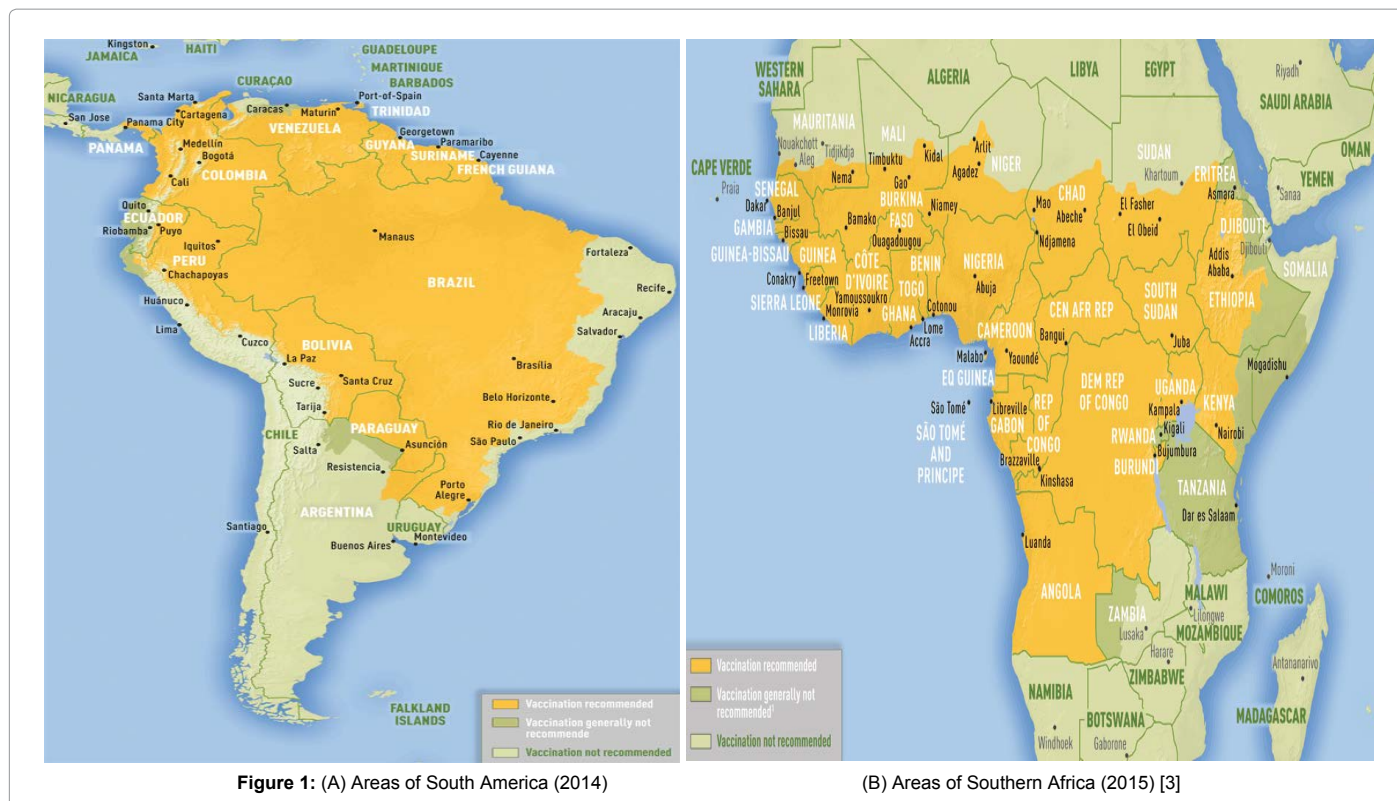
The first case of yellow fever virus infection was reported on December 5, 2015 from Viana municipality, Luanda Province. The situation on June 10, 2016 are reported 3,137 suspected cases in a country where 345 infected person deaths and 847 cases confirmed by laboratory analysis. The virus spread very quickly and in this situation

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started the vaccination of the population and in June almost half of country vaccinated and used 11,635,800 vaccines. Local transmission in 31 districts of 12 provinces and the majority cases were aged 15-24 yrs. The situation is a risk not only for transmission in other provinces, but also the exportation in other countries close to Angola.

WHO assessed the situation in Angola as concerning and need to be closely monitored to avoid deterioration [4].

The situation Democratic Republic of Congo (DR of Congo)

On 31 May reported 2016 700 suspected infection cases and 63 cases deaths. During this situation, collected 689 samples and samples sent to the lab for analysis, where 52 cases, lab confirmed for YF from 5 provinces: Congo Central-36 cases: Kinshasa 11 cases, Kwango 3 cases, Bas Uele 1 case, Tshuapa 1 case. Only 2 cases classified as autochthones

other imported from Angola 26 May 2200000 doses of vaccines. It is a risk for neighboring countries because of heavy population movement [5].

The situation Uganda and Kenya

Uganda 2016: The first signal for the outbreak of YFV infection was reported on 8 April in Masaka, south of Kampala, where 3 cases YFV infections from the single family in Masaka which confirmed by PCR test. On 26 March – 18 April were reported 30 suspected cases, include 7 deaths. The situation in DR Congo and Kenya were assessed from WHO in the context of international export of YF cases from Angola to China.

Kenya 2016: On March were reported 2 cases of YFV imported from Kenyan working in Angola, 1 case died and other recovered after hospitalization. The PCR test was negative response but anti- YF IgM positive. WHO assessed situation in Kenya as the risk minimal because the density of the component vector *Aedes aegypti*, in Nairobi is very low and 2 case did not arrive in a viraemic state [6].

China on 13 March, notified an imported case of YFV infection in country from Angola confirmed by PCR test. WHO assessed the situation as the minimal risk for transmission of infection because the season is not active for the competent vector. The conclusion of the situation is: YFV infection can spread very quickly as the cases in Angola, while for countries where the cases are imported from endemic areas has some factors that impact in spreading of the virus [7].

YF Vaccines and Vaccination in World

The vaccine against yellow fever virus was used in year 1930, produced from Asibi strain attenuated. The vaccines 17D use for preventing of Yellow fever virus infection and is successful vaccine, while the French Neurotropic vaccine used until 1982 and then stopped

because cause the neurotropic infection in vaccinated population. In Brazil manufactured and used the vaccines 17 DD manufactured. The USA manufactured the vaccine 17D-204 which is used in the USA and other countries for vaccination of the population. All vaccines against yellow fever virus have no differences in the immune response of vaccines. On 2008, in Burkina Faso, WHO, UNICEF, with the support of the GAVI launched the immunization campaign in 12 African at high risk countries for YF transmission 2006-2013. On November 8-9, 2008, 7.566218 people aged ≥ 9 months excluded pregnant women, critically ill patients, patients allergic to egg in 37 districts. The AEFI reported during the vaccination were not higher than previous reports.

Results of the Study

The campaign of vaccination in 8 African countries on years 2007-2010: Benin, Cameroon, Guinea, Liberia, Mali, Senegal, Sierra Leone and Togo, vaccinated approximately 38 million people with YFV and reported 3116 AEFI, where: 164 reports (5%) classified as serious, 22 reports (13%) classified as YF vaccine reactions, 11 reports (50%) hypersensitivity reactions, 6 (27%) suspected YEL-AND, 5 (23%) suspected YEL-AVD. The conclusion of this vaccination campaign was that active case finding in 8 different countries did not find any incidence of YF vaccine associated AEFI that was higher than previous reports and data confirm the safety of YF vaccines and support the using in the future the vaccination for prevention in endemic areas attenuated YF vaccine [8].

On 2011 in Brazil was performed the study involved 2.660.929 patients after vaccination. The Yellow Fever virus is endemic in the North and Central-West of Brazil. The results of the study show that no observed cases of viscerotropic, no observed cases neurotropic, only 1 case of anaphylaxis and 26 cases of urticaria (hypersensitivity). The AEFI observed for the target group: 2199 children; 1334 women; 174 patients with HIV+ were no serious. The conclusions for this study were, PCR amplicon sequencing needed to prove the AEFI reported were caused from YF vaccine and YF vaccine proves to be very safe and highly effective against very dangerous illness with high mortality.

GAVI for the years 2011-2020 planed vaccination of 174 million people in South Africa and South America to prevent the infection of yellow fever virus. On 2012, based on the study for safety of yellow fever vaccines 17 D, 17DD (Brazil), 17 D-204 for vulnerable group as infants and children, pregnant and breastfeeding women, patient with human immunodeficiency virus positive, and persons >60 years old rare serious adverse events after vaccination, include neurologic or viscerotropic syndromes or anaphylaxis and patients treated with immunosuppressive medications resulted neurotropic diseases and anaphylaxis for persons >60 years old, 2 serious AE in maternal-neonate transmission and very small cases with viscerotropic diseases and no other case was identified [9-13].

Based on the data the suspected AEFI of yellow fever vaccines reported in VAERS(spontaneous reports) CDC- USA and data from reporting in VigiBase UMC (Uppsala Monitoring Center-spontaneous reports), which is center for reporting of AEFI from all world can show the results in Figure 2 for the last 5 years. As we can see from the charter has no increasing of number reporting.

Conclusion

The vaccine against yellow fever virus is recommended to be used for vaccination of people ≥ 9 months old and the vaccination provides long-lasting immunity. The number of vaccinations is increasing around the world and the reported data resulted the vaccine is

qualifying very safe and efficacious. The recommendation of WHO and the results of studies performed show that the vaccine against yellow fever virus is the best way for the prevention of yellow fever infection, not only for people in endemic countries, but and for people travelling in these countries can also apply the vaccination. The people of age <6 months and ≥ 60 years, immune deficiency, women who breastfeeding, people allergic to egg, immune suppression, thymus diseases, pregnant women are sensitive from live attenuated 17 D vaccine. The vaccine against yellow fever virus is safe and no serious AEFI related to Associated Neurotropic Diseases (AND) and viscerotropic (AVD) diseases. All vaccines against yellow fever virus used today in the world have high efficacy and almost the same.

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