

Yellow fever vaccines: Selected references for the WHO Position Paper published 3 Oct 2003

Background information on yellow fever

Robertson SE, Hull BP, Tomori O, Bele O, LeDuc JW, Esteves K. Yellow fever: a decade of reemergence. JAMA. 1996 Oct 9;276(14):1157-62

Since the 1980s, yellow fever has reemerged across Africa and in South America. The total of 18 735 yellow fever cases and 4522 deaths reported from 1987 to 1991 represents the greatest amount of yellow fever activity reported to the World Health Organization (WHO) for any 5-year period since 1948. There is an excellent vaccine against yellow fever. At present, a high proportion of travelers to at-risk areas are reported to be immunized, reflecting widespread knowledge about the International Health Regulations. In South America, yellow fever remains an occupational hazard for forest workers, who should be immunized. However, *Aedes aegypti* mosquitoes are now present in urban areas in the Americas (including southern parts of the United States), and there is concern that yellow fever could erupt in explosive outbreaks. In Africa, a large proportion of cases have occurred in children. The WHO, the United Nations Children's Fund (UNICEF), and the World Bank have recommended that 33 African countries at risk for yellow fever add the vaccine to the routine Expanded Programme on Immunization; studies show that this would be highly cost-effective. To date, financing yellow fever vaccine has been a major problem for these countries, which are among the poorest in the world. For this reason, WHO has launched an appeal to raise \$70 million for yellow fever control in Africa.

Mutebi JP, Barrett AD. The epidemiology of yellow fever in Africa. Microbes Infect. 2002 Nov;4(14):1459-68.

Yellow fever (YF) is still a major public health problem, particularly in Africa, despite the availability of a very efficacious vaccine. The World Health Organization estimates that there are 200,000 cases of YF annually, including 30,000 deaths, of which over 90% occur in Africa. In the past 15 years, the number of YF cases has increased tremendously, with most of the YF activity in West Africa. This increase in YF activity is in part due to a breakdown in YF vaccination and mosquito control programs. Five genotypes of YF virus have been found in Africa, and each genotype circulates in a distinct geographical region. West Africa genotype I, found in Nigeria and surrounding areas, is associated with frequent epidemics, whereas the three genotypes in East and Central Africa are in regions where YF outbreaks are rare. Other factors, including genetic and behavioral variation among vector species, are also thought to play a role in the epidemiology of YF in Africa.

Monath TP. Yellow fever: an update. Lancet Infect Dis. 2001 Aug;1(1):11-20.

Yellow fever, the original viral haemorrhagic fever, was one of the most feared lethal diseases before the development of an effective vaccine. Today the disease still affects as many as 200,000 persons annually in tropical regions of Africa and South America, and poses a significant hazard to unvaccinated travellers to these areas. Yellow fever is transmitted in a cycle involving monkeys and mosquitoes, but human beings can also serve as the viraemic host for mosquito infection. Recent increases in the density and distribution of the urban mosquito vector, *Aedes aegypti*, as well as the rise in air travel increase the risk of introduction and spread of yellow fever to North and Central America, the Caribbean and Asia. Here I review the clinical features of the disease, its pathogenesis and pathophysiology. The disease mechanisms are poorly understood and have not been the subject of modern clinical research. Since there is no specific treatment, and management of patients with the disease is extremely problematic, the emphasis is on preventative vaccination. As a zoonosis, yellow fever cannot be eradicated, but reduction of the human disease burden is achievable through routine childhood vaccination in endemic countries, with a low cost for the benefits obtained. The biological characteristics, safety, and efficacy of live attenuated, yellow fever 17D vaccine are reviewed. New applications of yellow fever 17D virus as a vector for foreign genes hold considerable promise as a means of developing new vaccines against other viruses, and possibly against cancers.

Yellow fever vaccines

Pugachev KV, Ocran SW, Guirakhoo F, Furby D, Monath TP. Heterogeneous nature of the genome of the ARILVAX yellow fever 17D vaccine revealed by consensus sequencing. Vaccine. 2002 Jan 15;20(7-8):996-9.

Consensus sequencing of the genome of the ARILVAX live attenuated yellow fever (YF) 17D vaccine was performed directly on reconstituted virus from a vial of the vaccine secondary seed (without plaque-purification or cloning of cDNA). The genome of ARILVAX was identical in organization and size (10,862 nucleotides (nt)) to other published YF 17D sequences. A total of 12 nt heterogeneities were detected indicating that the vaccine is a heterogeneous population. Some of these indicated the presence of quasispecies with residues not reported previously for other sequenced YF 17D strains. A number of nts clearly differed from some YF vaccine strain sequences but coincided with the others, which could be due to the use of consensus sequencing approach in this study. Most (but not all) of the heterogeneities and nt differences were silent (i.e. did not result in an amino acid change). The differences are inconsequential to safety and effectiveness of ARILVAX. Other YF 17D vaccines are undoubtedly also heterogeneous and need to be re-examined using the consensus approach.

Reinhardt B, Jaspert R, Niedrig M, Kostner C, L'age-Stehr J. Development of viremia and humoral and cellular parameters of immune activation after vaccination with yellow fever virus strain 17D: a model of human flavivirus infection. J Med Virol. 1998 Oct;56(2):159-67.

To monitor early and late events of immune system activation after primary and secondary flavivirus infection, 17 healthy persons were vaccinated with the standard 17D vaccine virus strain of yellow fever (YF). Twelve of these persons had not received YF vaccine previously and 5 had been vaccinated once at least 10 years before. Viremia and various parameters of humoral and cellular immune activation were followed daily for 7 days and weekly thereafter. Viremia was detected by reverse transcriptase-polymerase chain reaction in all 12 first-time vaccinees beginning from the second to the sixth day after vaccination; most tested positive between the fourth and sixth day. Infectious 17D virus was detected using a plaque forming assay in the serum of 7 of the 12 first-time vaccinees. As first parameters of immune activation, neopterin and beta2-microglobulin markedly increased between day 2 and day 6 postvaccination. In parallel to the viremia, circulating CD8+ T-cells significantly increased, with peak levels at day 5 after primary vaccination, indicating an activation of the cellular immune system. Neither viremia nor significant changes of these activation markers were observed in the five revaccinated persons. Neutralizing antibodies directed against the 17D vaccine strain developed in all persons within 2 weeks after vaccination. No correlation was found between the extent of viremia and the titer of neutralizing antibodies. Revaccination was followed by a minor and transient increase of neutralizing antibodies. High titers of neutralizing antibodies persisted for at least 10 years after primary vaccination.

Co MD, Terajima M, Cruz J, Ennis FA, Rothman AL. Human cytotoxic T lymphocyte responses to live attenuated 17D yellow fever vaccine: identification of HLA-B35-restricted CTL epitopes on nonstructural proteins NS1, NS2b, NS3, and the structural protein E. Virology. 2002 Feb 1;293(1):151-63.

Yellow fever virus (YFV) is a re-emerging problem despite the existence of an effective live-attenuated vaccine. The induction of YFV-neutralizing antibodies undoubtedly contributes to vaccine efficacy, but T lymphocyte responses to YFV likely play a role in long-term efficacy. We studied the T lymphocyte responses to YFV in four vaccinees. Proliferation and cytolytic responses to YFV were demonstrated in all subjects. We isolated 13 YFV-specific CD8(+) CTL lines that recognized epitopes on the E, NS1, NS2b, and NS3 proteins; eight CTL lines were HLA-B35-restricted. YFV-specific T cell responses were detectable by IFN gamma ELISPOT assays 14 days postvaccination, with T cell frequencies sustained for up to 19 months. To our knowledge, this is the first report of human T lymphocyte responses following YFV vaccination. These results indicate that the live 17D YFV vaccine induced CD8(+) T cell responses directed against at least four different HLA-B35-restricted YFV epitopes.

Niedrig M, Lademann M, Emmerich P, Lafrenz M. Assessment of IgG antibodies against yellow fever virus after vaccination with 17D by different assays: neutralization test, haemagglutination inhibition test, immunofluorescence assay and ELISA. Trop Med Int Health. 1999 Dec;4(12):867-71.

We analysed serum samples of 209 subjects immunized with yellow fever vaccine 17D by different assays: neutralization test, immunofluorescence assay, haemagglutination inhibition test and ELISA, for presence of 17D-specific antibodies. Serum samples were taken from a few weeks up to 35 years after vaccination. The neutralization test had the highest sensitivity. There was no correlation of results between the serological assays. Considering NT titres > 1:10 as indicating protection, we found that about 75% of subjects remained immune even 10 years after vaccination, with a median NT titre of 1:40 in reactive sera.

Monath TP, Nichols R, Archambault WT, Moore L, Marchesani R, Tian J, Shope RE, Thomas N, Schrader R, Furby D, Bedford P. Comparative safety and immunogenicity of two yellow fever 17D vaccines (ARILVAX and YF-VAX) in a phase III multicenter, double-blind clinical trial. Am J Trop Med Hyg. 2002 May;66(5):533-41.

Yellow fever (YF) is a significant health problem in South America and Africa. Travelers to these areas require immunization. The United States, infested with *Aedes aegypti* mosquitoes, is at risk of introduction of this disease. There is only a single U.S. manufacturer of YF 17D vaccine, and supplies may be insufficient in an emergency. A randomized, double-blind outpatient study was conducted in 1,440 healthy individuals, half of whom received the U.S. vaccine (YF-VAX) and half the vaccine manufactured in the United Kingdom (ARILVAX). A randomly selected subset of approximately 310 individuals in each treatment group was tested for YF neutralizing antibodies 30 days after vaccination. The primary efficacy endpoint was the proportion of individuals who developed a log neutralization index (LNI) of 0.7 or higher. Seroconversion occurred in 98.6% of individuals in the ARILVAX group and 99.3% of those in the YF-VAX group. Statistically, ARILVAX was equivalent to YF-VAX ($P = .001$). Both vaccines elicited mean antibody responses well above the minimal level (LNI 0.7) protective against wild-type YF virus. The mean LNI in the YF-VAX group was higher (2.21) than in the ARILVAX group (2.06; $P = .010$) possibly because of the higher dose contained in YF-VAX. Male gender, Caucasian race, and smoking were associated with higher antibody responses. Both vaccines were well tolerated. Overall, the treatment groups were comparable with respect to safety except that individuals in the ARILVAX group experienced significantly less edema, inflammation, and pain at the injection site than those in the YF-VAX group. No serious adverse events were attributable to either vaccine. YF-VAX participants (71.9%) experienced one or more nonserious adverse events than ARILVAX individuals (65.3%; $P = .008$). The difference was due to a higher rate of injection site reactions in the YF-VAX group. Mild systemic reactions (headache, myalgia, malaise, asthenia) occurred in roughly 10% to 30% of participants during the first few days after vaccination, with no significant difference across treatment groups. Adverse

events were less frequent in individuals with preexisting immunity to YF, indicating a relationship to virus replication.

Cetron MS, Marfin AA, Julian KG, Gubler DJ, Sharp DJ, Barwick RS, Weld LH, Chen R, Clover RD, Deseda-Tous J, Marchessault V, Offit PA, Monath TP. Yellow fever vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2002. MMWR Recomm Rep. 2002 Nov 8;51(RR-17):1-11.

This report updates CDC's recommendations for using yellow fever vaccine (CDC. Yellow Fever Vaccine: Recommendations of the Advisory Committee on Immunizations Practices: MMWR 1990;39[No. RR-6]1-6). The 2002 recommendations include new or updated information regarding 1) reports of yellow fever vaccine-associated viscerotropic disease (previously reported as febrile multiple organ system failure); 2) use of yellow fever vaccine for pregnant women and persons infected with human immunodeficiency virus (HIV); and 3) concurrent use of yellow fever vaccine with other vaccines. A link to this report and other information related to yellow fever can be accessed at the website for Travelers' Health, Division of Global Migration and Quarantine, National Center for Infectious Diseases, CDC, at <http://www.cdc.gov/travel/index.htm>, and through the website for the Division of Vector-Borne Infectious Diseases, National Center for Infectious Diseases, CDC, at <http://www.cdc.gov/ncidod/dvbid/yellowfever/index.htm>.

Stefano I, Sato HK, Pannuti CS, Omoto TM, Mann G, Freire MS, Yamamura AM, Vasconcelos PF, Oselka GW, Weckx LW, Salgado MF, Noale LF, Souza VA. Recent immunization against measles does not interfere with the sero-response to yellow fever vaccine. Vaccine. 1999 Mar 5;17(9-10):1042-6.

In order to determine whether previous measles vaccination interferes with the sero-response to yellow fever vaccine, 294 children at nine months of age were randomly assigned to immunization with yellow fever vaccine at different time intervals after measles vaccination. The seroconversion rate (SCR) and the log₁₀ geometric mean titer (GMT) for 17 DD yellow fever vaccine at different intervals after Schwarz measles vaccination were: 1-6 days: SCR = 44/57 = 77%; GMT = 4.57; 7-13 days: SCR = 36/53 = 68%; GMT = 4.46; 14-21 days: SCR = 55/65 = 85%; GMT = 4.46; 22-27 days: SCR = 41/54 = 76%; GMT = 4.41 and >28 days: SCR = 52/65 = 80%; GMT = 4.24 ($p > 0.05$). We conclude that recent immunization against measles does not interfere with the sero-response to yellow fever vaccine.

YF vaccination of travellers

Monath TP, Cetron MS. Prevention of yellow fever in persons traveling to the tropics. Clin Infect Dis. 2002 May 15;34(10):1369-78. Epub 2002 Apr 25. (Erratum in: Clin Infect Dis 2002 Jul 1;35(1):110)

Yellow fever (YF) is a potentially lethal mosquito-borne viral hemorrhagic fever endemic in Africa and South America. Nine million tourists annually arrive in

countries where YF is endemic, and fatal cases of YF have occurred recently in travelers. In this article, we review the risk factors for YF during travel and the use of YF 17D vaccine to prevent the disease. Although the vaccine is highly effective and has a long history of safe use, the occurrence of rare, fatal adverse events has raised new concerns. These events should not deter travelers to areas where YF is endemic from being immunized, because the risk of YF infection and illness may be high in rural areas and cannot be easily defined by existing surveillance. To avoid unnecessary vaccination, physicians should vaccinate persons at risk on the basis of knowledge of the epidemiology of the disease, reports of epidemic activity, season, and the likelihood of exposure to vector mosquitoes.

Adverse reaction to YF vaccination

Arya SC. Yellow fever vaccine safety: a reality or a myth? *Vaccine*. 2002 Nov 1;20(31-32):3627-8.

The 17D-derived yellow fever (YF) vaccines have had an excellent record of their safety among millions of recipients. Recently, extensive viral dissemination in seven vaccinees, aged 5-79 years, with just one survivor posed a serious challenge for vaccine manufacturers. Prospective evaluations of yellow fever vaccine bulk suspensions for their viscerotropism and neurovirulence in primates or an alternate animal should minimize identical viral dissemination among prospective recipients of YF vaccines.

Galler R, Pugachev KV, Santos CL, Ocran SW, Jabor AV, Rodrigues SG, Marchevsky RS, Freire MS, Almeida LF, Cruz AC, Yamamura AM, Rocco IM, da Rosa ES, Souza LT, Vasconcelos PF, Guirakhoo F, Monath TP. Phenotypic and molecular analyses of yellow fever 17DD vaccine viruses associated with serious adverse events in Brazil. *Virology*. 2001 Nov 25;290(2):309-19.

The yellow fever (YF) 17D virus is one of the most successful vaccines developed to date. Its use has been estimated to be over 400 million doses with an excellent record of safety. In the past 3 years, yellow fever vaccination was intensified in Brazil in response to higher risk of urban outbreaks of the disease. Two fatal adverse events temporally associated with YF vaccination were reported. Both cases had features similar to yellow fever disease, including hepatitis and multiorgan failure. Two different lots of YF 17DD virus vaccine were administered to the affected patients and also to hundreds of thousands of other individuals without any other reported serious adverse events. The lots were prepared from the secondary seed, which has been in continuous use since 1984. Nucleotide sequencing revealed minor variations at some nucleotide positions between the secondary seed lot virus and the virus isolates from patients; these differences were not consistent across the isolates, represented differences in the relative amount of each nucleotide in a heterogeneous position, and did not result in amino acid substitutions. Inoculation of rhesus monkeys with the viruses isolated from the two patients by the intracerebral (ic) or intrahepatic (ih) route caused minimal viremia and no clinical signs of infection or alterations in laboratory markers. Central nervous system histological scores of rhesus monkeys inoculated ic

were within the expected range, and there were no histopathological lesions in animals inoculated ih. Altogether, these results demonstrated the genetic stability and attenuated phenotype of the viruses that caused fatal illness in the two patients. Therefore, the fatal adverse events experienced by the vaccinees are related to individual, genetically determined host factors that regulate cellular susceptibility to yellow fever virus. Such increased susceptibility, resulting in clinically overt disease expression, appears to be extremely rare.

Martin M, Tsai TF, Cropp B, Chang GJ, Holmes DA, Tseng J, Shieh W, Zaki SR, Al-Sanouri I, Cutrona AF, Ray G, Weld LH, Cetron MS. Fever and multisystem organ failure associated with 17D-204 yellow fever vaccination: a report of four cases. Lancet. 2001 Jul 14;358(9276):98-104

BACKGROUND: In 1998, the US Centers for Disease Control and Prevention was notified of three patients who developed severe illnesses days after yellow fever vaccination. A similar case occurred in 1996. All four patients were more than 63 years old. **METHODS:** Vaccine strains of yellow fever virus, isolated from the plasma of two patients and the cerebrospinal fluid of one, were characterised by genomic sequencing. Clinical samples were subjected to neutralisation assays, and an immunohistochemical analysis was done on one sample of liver obtained at biopsy. **FINDINGS:** The clinical presentations were characterised by fever, myalgia, headache, and confusion, followed by severe multisystemic illnesses. Three patients died. Vaccine-related variants of yellow fever virus were found in plasma and cerebrospinal fluid of one vaccinee. The convalescent serum samples of two vaccinees showed antibody responses of at least 1:10240. Immunohistochemical assay of liver tissue showed yellow fever antigen in the Kupffer cells of the liver sample. **INTERPRETATION:** The clinical features, their temporal association with vaccination, recovery of vaccine-related virus, antibody responses, and immunohistochemical assay collectively suggest a possible causal relation between the illnesses and yellow fever vaccination. Yellow fever remains an important cause of illness and death in South America and Africa; hence, vaccination should be maintained until the frequency of these events is quantified.

WHO documents on YF/YF vaccines

WHO documents on vaccines are found under <http://www.who.int/immunization/en/>