Summaries of papers cited in: 'Vaccines and vaccination against Yellow Fever: WHO Position Paper – June 2013'

Breugelmans JG et al: Reporting rates in mass campaigns *Vaccine*, 2001, 31(14):1819-1829

Serious, but rare, adverse events following immunization (AEFI) have been reported with yellow fever (YF) 17D vaccine. These include severe allergic reactions, YF vaccine-associated neurologic disease (YEL-AND) and YF vaccine-associated viscerotropic disease (YEL-AVD). The frequency with which YEL-AND and YEL-AVD occur in YF endemic countries is mostly unknown. From 2007 to 2010, eight African countries – Benin, Cameroon, Guinea, Liberia, Mali, Senegal, Sierra Leone, and Togo- implemented large-scale YF preventive vaccination campaigns. Each country established vaccine pharmacovigilance systems that included standard case definitions, procedures to collect and transport biological specimens, and National Expert Committees to review data and classify cases. Staff in all countries received training and laboratory capacity was expanded. In total, just over 38 million people were vaccinated against YF and 3116 AEFIs were reported of which 164 (5%) were classified as serious. Of these, 22 (13%) were classified as YF vaccine reactions, including 11 (50%) hypersensitivity reactions, six (27%) suspected YEL-AND, and five (23%) suspected YEL-AVD. The incidence per 100,000 vaccine doses administered was 8.2 for all reported AEFIs, 0.43 for any serious AEFI, 0.058 for YF vaccine related AEFIs, 0.029 for hypersensitivity reactions, 0.016 for YEL-AND, and 0.013 for YEL-AVD. Our findings were limited by operational challenges, including difficulties in obtaining recommended biological specimens leading to incomplete laboratory evaluation, unknown case ascertainment, and variable levels of staff training and experience. Despite the limitations, active case-finding in the eight different countries did not find an incidence of YF vaccine associated AEFIs that was higher than previous reports. These data reinforce the safety profile of YF vaccine and support the continued use of attenuated YF vaccine during preventive mass vaccination campaigns in YF endemic areas.

Cavalcanti DP, et al: Early exposure to yellow fever vaccine during pregnancy. *Tropical Medicine & International Health,* 2007; 12: 833-837

This study investigated the association between use of yellow fever vaccine (YFV) during pregnancy and congenital malformations in exposed babies. An observed/expected frequencies study performed before and after the YF vaccination campaign was designed. 304 babies exposed to YFV during the prenatal period underwent physical examination to assess congenital abnormalities. The expected malformation frequencies were obtained from a reference population of 10 691 babies born in the same region and during the period immediately prior to

the vaccination campaign. These frequencies were evaluated using the Poisson distribution model. The major malformation rate found in this study was 3.3% (CI 1.7–6.3%). Minor abnormalities, especially naevi, were significantly more frequent ($P < 0.001$) than in the reference population. These data provide no indication that immunization with YFV early in pregnancy increases the risk of major malformations. The association found between YFV during pregnancy and minor malformations, especially pigmented naevi, may be due to evaluation bias. We suggest, nevertheless, that a reproductive risk hypothesis regarding minor malformations should be considered in future studies involving YFV.

de Filippis AM et al: Isolation and characterization of wild type yellow fever in cases temporarily associated with 17DD vaccination during an outbreak of yellow fever in Brazil. *Vaccine,* 2004, 22, 1073-1078

In 2001, a mass vaccination campaign was carried out in the state of Minas Gerais, southeast Brazil, to control an outbreak of sylvatic yellow fever (YF). During the outbreak, the surveillance system identified two fatal cases temporally associated with YF vaccination. Virus recovered from blood and postmortem samples from both individuals was identified as YF virus (YFV). Partial nucleotide sequencing was employed to characterize the origin of YFV in both cases. Wild-type YFV was identified as the aetiologic agent responsible for the disease

Garske et al: 2013, manuscript in preparation

Although eradication of yellow fever (YF) is not possible due to the wildlife reservoir, large scale vaccination carried out during the 1940s to 1960s in Africa reduced YF incidence for several decades. Following a period of low vaccination coverage, YF has resurged in Africa. Since 2006 there has been substantial funding for large preventive mass vaccination campaigns in twelve of the most affected countries in Africa to curb the rising burden of disease and control future outbreaks. This study used generalized linear regression models fitted to a dataset giving the locations of yellow fever outbreaks within the last 25 years to estimate the probability of outbreak reports across the endemic zone. Environmental variables and indicators for the surveillance quality in the affected countries were used as covariates. By comparing probabilities of outbreak reports estimated in the regression with the force of infection estimated for a limited set of locations for which serological surveys were available, the detection probability per case and the force of infection were estimated across the endemic zone. From this, the yellow fever burden in Africa was estimated for the year 2013 as 130,000 (95% CI 84,000 – 170,000) cases with fever, jaundice or haemorrhage and 44,000 (95% CI 29,000 – 60,000) deaths, taking into account the current level of vaccination coverage. The recent mass vaccination campaigns are estimated to have reduced the burden by 27% (95% CI 23 - 30%) across the region, achieving an up to 82% reduction in countries targeted by these campaigns.

Gibney et al: Detection of anti-Yellow Fever Virus Immunoglobulin M Antibodies at 3-4 Years Following Yellow Fever Vaccination, *American Journal of Tropical Medicine and Hygiene*, 2012, 87:1112-1115

The duration of anti-yellow fever (YF) virus immunoglobulin M (IgM) antibodies following YF vaccination is unknown, making it difficult to interpret positive IgM antibody results in previously vaccinated travellers. This study evaluates the frequency and predictors of YF IgM antibody positivity 3–4 years following YF vaccination. Twenty-nine (73%) of 40 participants had YF IgM antibodies 3–4 years post-vaccination. No demographic or exposure variables were predictive of YF IgM positivity. However, persons who were YF IgM positive at 3–4 years post-vaccination had earlier onset viraemia and higher neutralizing antibody geometric mean titres at 1 month and 3–4 years post-vaccination compared with persons who were YF IgM negative. Detection of YF IgM antibodies several years post-vaccination might reflect remote YF vaccination rather than recent YF vaccination or YF virus infection.

Izurieta, RO: Anamnestic immune response to dengue and decreased severity of yellow fever. *Journal of Global Infectious diseases*, 2009. 1:111-116.

It has been hypothesized that protective immunity against yellow fever (YF) from cross-reactive dengue antibodies may explain the absence of YF in Southern Asia, where dengue immunity is almost universal. This cross-sectional study evaluates the association between protective immunity from cross-reactive dengue antibodies with YF infection and severity of the disease. Interviews and serology were used to investigate a population of military personnel in a jungle garrison located in the Ecuadorian Amazonian rainforest. A log-linear regression analysis was used to evaluate the age and presence of antibodies against the dengue type 2 virus as predictors of YF infection or severe disease. Dengue antibodies were observed in 77.3% of YF cases from the coastal region where dengue is endemic; in 14.3% cases from the Amazon; and in 16.7 % cases from the Andean region. Dengue cross-reactive antibodies were not significantly associated with YF infection but were significantly associated with severity of the disease. Previous exposure to dengue virus may induce an anamnestic immune response that does not prevent YF infection but greatly reduces the severity of the disease.

Khromava et al. Yellow fever vaccine: an updated assessment of advanced age as a risk factor for serious adverse events. *Vaccine,* 2005, 23(25); 3256-3263

Since 1996, there have been 14 reports of yellow fever vaccine (YEL)-associated viscerotropic disease (YEL-AVD) cases and four reports of YEL-associated neurotropic disease (YEL-AND) worldwide, changing our understanding of the risks of the vaccine. This study analyses 722 adverse event reports after YEL submitted to the U.S. Vaccine Adverse Event Reporting System in 1990–2002, updating estimates of the age-adjusted reporting rates of serious adverse events,

YEL-AVD and YEL-AND. Reporting rates of serious adverse events were significantly higher among vaccinees aged ≥60 years than among those 19–29 years of age (reporting rate ratio = 5.9, 95% CI 1.6–22.2). For elderly travellers, the risk of severe illness and death due to YF infection should be balanced against the risk of a serious adverse event due to YEL

Kirk R: Epidemic of yellow fever in Nuba Mountains, Anglo-Egyptian Sudan. *Annals of Tropical Medicine*, 1941, 35: 67–113.

This article describes the natural history of yellow fever and clinical outcomes seen during an epidemic in the Nuba Mountains of what was then Anglo-Egyptian Sudan.

Lindsey NP et al: Adverse event reports following yellow fever vaccination. Vaccine, 2008, 26(48): 6077-6082

Yellow fever (YF) vaccine has been used for prevention of YF since 1937 with over 500 million doses administered. However, rare reports of severe adverse events following vaccination have raised concerns about the vaccine's safety. This study reviewed reports of adverse events following YF vaccination reported to the U.S. Vaccine Adverse Event Reporting System (VAERS) from 2000 to 2006. Estimates of age and sex distribution of administered doses obtained from a 2006 survey of authorized vaccine providers were used to calculate age- and sex-specific reporting rates of all serious adverse events (SAE), anaphylaxis, YF vaccine-associated neurotropic disease, and YF vaccine-associated viscerotropic disease. Reporting rates of SAEs were substantially higher in males and in persons aged ≥60 years. These findings reinforce the generally acceptable safety profile of YF vaccine, but highlight the importance of physician and traveller education regarding the risks and benefits of YF vaccination, particularly for travellers ≥60 years of age. Vaccination should be limited to persons travelling to areas where the risk of YF is expected to exceed the risk of serious adverse events after vaccination, or if not medically contraindicated, where national regulations require proof of vaccination to prevent introduction of YF.

de Menezes Martins R et al: Yellow Fever vaccine post-marketing surveillance in Brazil. *Procedia in Vaccinology*, 2010, 2: 178-183.

Viscerotropic disease, a disease with high mortality, results from the dissemination of the yellow fever vaccine virus throughout the body. Following vaccination with the Bio-Manguinhos 17DD vaccine, 26 cases of viscerotrophic disease 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 but could be related to the existence of autoimmune diseases, such as systemic lupus erythematosus. Adverse neurological events seen after yellow fever vaccination

include aseptic meningitis, encephalitis, and autoimmune neurological events such as Guillain-Barré syndrome. In Rio Grande do Sul (2009) 2 cases of confirmed meningoencephalitis occurred in newborns after yellow fever vaccination of a breastfeeding mother. Bio-Manguinhos/Fiocruz is now carrying out a dose-response study to determine whether the vaccine can be administered in a lower dose in order to improve safety. In addition, further purification of the current vaccine, and studies into development of a non-live yellow fever vaccine are under way.

Monath, TPC: Neutralizing antibody responses in the major immunoglobulin classes to yellow fever 17D vaccination of humans. ***American Journal of Epidemiology, 1971,*** **93: 122–129.**

This study measured the antibody response in individual immunoglobulin fractions in human volunteers vaccinated with yellow fever (YF) 17D virus. Sera were fractionated by gel filtration; neutralizing antibodies were measured by a constant virus-serum dilution plaque reduction technique in BHK-21 cell cultures. In whole sera, neutralizing antibodies were present by the eighth day following vaccination. IgM antibodies were first detected on days 8 or 9, rose to high titres between days 14 and 17, and tended to decline gradually thereafter. During the first 4–6 weeks following vaccination, IgM antibody titres were 16- to-256-fold higher than IgG antibody titres. Significant amounts of IgM antibody were present for as long as 82 days following primary vaccination. IgG antibodies appeared later than IgM antibodies, (between 10 and 17 days after vaccination), tended to-remain stable or to rise slightly thereafter, and did not surpass IgM titres. IgM antibody was present in significant amounts 18 months after the last vaccination in an individual with multiple prior exposures to YF 17D virus. For both IgM and IgG antibodies, a high degree of specificity was demonstrated in neutralization tests using various strains of YF virus and heterologous Group B Arboviruses. The prolonged synthesis of IgM antibody suggested persistence of antigen stimulation.

Monath TP. Yellow fever: an update. ***Lancet Infectious diseases,*** **2001, 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 have increased the risk of introduction and spread of YF to North and Central America, the Caribbean, and Asia. YF 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, YF 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. New applications of YF 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.

Monath TP, Cetron MS: Prevention of Yellow fever in persons traveling to the tropics. *Clinical infectious diseases*, 2002, 34: 1369-1378

Although YF 17D 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 travellers 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.

Monath TP, Nasidi A. Should yellow fever vaccine be included in the expanded program of immunization in Africa? A cost-effectiveness analysis for Nigeria, *The American Journal of Tropical Medicine and Hygiene*, 1993, 48 (2): 274-299

The cost-effectiveness of preventive yellow fever vaccination versus emergency mass vaccination campaigns for epidemic control remains a matter of controversy. Until recently, Nigeria and other Anglophone countries in West Africa most severely afflicted by yellow fever epidemics have followed a policy of emergency control. The effects of including yellow fever 17D vaccine in the Expanded Program of Immunization (EPI) on the immune status of the Nigerian population was studied under conservative assumptions of vaccine coverage and efficacy. The model defined the age-specific prevalence of immunity resulting from vaccination of infants and from natural endemic infection beginning in 1991 and extending over a time horizon of 35 years. The data were used to predict the number of cases and deaths during hypothetical epidemics in 2006 and 2026, representing the historic periodicity of epidemics. A second model was used to demonstrate that a > or = 60% prevalence of immunity would preclude epidemic yellow fever transmission. Under base case assumptions, this prevalence would be reached after 18 years of initiating routine yellow fever vaccination in the Guinea savannah zone, the region most often affected by epidemics. Using assumptions based on data from other African countries, the cost of adding yellow fever vaccine to the existing EPI was estimated as +0.65 per fully immunized child, whereas the cost of emergency vaccination in the face of an epidemic was estimated as +7.84/person. Vaccine coverage rates achievable by the EPI were modelled on recent successes with measles vaccine, and began in 1991 at 60%. The effective vaccine coverage rate in an emergency campaign was taken as 10%, based on recent experience. For an epidemic of moderate size in 2006 (morbidity similar to the documented outbreak in 1987), the cost-effectiveness of emergency mass immunization for control of hypothetical yellow fever epidemics was two-fold higher ($381/case and $1,904/death prevented) than that of the EPI ($763/case and $3,817/death prevented). However, despite its higher cost, the efficiency of the EPI was seven-fold greater in terms of cases and deaths

prevented. In large epidemics, such as those occurring over successive years (1986-1991) in Nigeria, cost-effectiveness of the EPI exceeded that of emergency control. The EPI may also play an important role in the prevention of endemic yellow fever. Assuming annual rates of endemic yellow fever predicted by serologic surveys, routine vaccination would significantly reduce morbidity and mortality at cost-effectiveness ratios within the range for other diseases prevented by the EPI, including polio, tetanus, and diphtheria.

Monath TP et al: Comparative safety and immunogenicity of two yellow fever 17D vaccines (ARILVAX and YF-VAX) in a phase III, multicenter, double blind clinical trial. ***American Journal of Tropical Medicine and Hygiene,*** **2002, 66 (5): 533–541.**

A randomized, double-blind outpatient study was conducted in 1,440 healthy individuals, half of whom received the U.S. vaccine (YF-VAX) while the other half received 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 oedema, 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 non-serious adverse events than ARILVAX individuals (65.3%; P = .008) due to a higher rate of injection site reactions in the YF-VAX group. Mild systemic reactions (headache, myalgia, malaise, aesthenia) 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.

Nascimento Silva JR et al. Mutual interference on the immune response to yellow fever vaccine and a combined vaccine against measles mumps and rubella. Vaccine, 2011, 29(3): 6327–6334.

This study used a randomized trial to assess the immunogenicity and reactogenicity of yellow fever vaccines (YFV) given with combined measles–mumps–rubella (MMR) vaccines, either simultaneously in separate injections, or 30 days or more after. Volunteers were also randomized to YFV produced from 17DD and WHO-17D-213 substrains. The study group comprised 1769 healthy 12-month-old children brought to health care centres in Brasilia for routine vaccination. The reactogenicity was of the type and frequency expected for the vaccines and no severe

adverse events were associated with either vaccine. Seroconversion and seropositivity were similar across both groups 30 days or more after vaccination. Subjects injected with YFV and MMR simultaneously had lower seroconversion rates – 90% for rubella, 70% for yellow fever and 61% for mumps – compared with those vaccinated 30 days apart – 97% for rubella, 87% for yellow fever and 71% for mumps. Seroconversion rates for measles were higher than 98% in both comparison groups. Geometric mean titres (GMT) for rubella and for yellow fever were approximately three times higher among those who got the vaccines 30 days apart. For measles and mumps antibodies GMTs were similar across groups. Interference by MMR in the immune response to YFV and YFV's interference in the immune response to the rubella and mumps components of the MMR have never been reported. Nevertheless, these results are consistent with previous observations from other live vaccines and may affect the recommendations regarding primary vaccination with yellow fever vaccine and MMR.

Nasidi A et al: Yellow fever vaccination and pregnancy: a four-year prospective study. ***Transactions of the Royal Society of Tropical Medicine and Hygiene,*** **1993, 87(3):337-339**

During an outbreak of yellow fever (YF) in Nigeria from 1986–87, women at various stages of pregnancy were vaccinated against YF, either because those pregnancies were not known at the time or because they requested vaccination out of fear of acquiring the disease. This offered an opportunity to assess the safety and efficacy of YF vaccine in pregnant women and the effect of this vaccine on their newborn children. Pre-vaccination and post-vaccination serum samples from the vaccinated pregnant women were tested by enzyme-linked immunosorbent assay and by neutralization tests for antibody to YF virus. The results showed that the antibody responses of these pregnant women were much lower than those of YF-vaccinated, non-pregnant women in a comparable control group. Follow-up of these women and their newborn children for 3–4 years showed no abnormal effects that could be attributed to the YF vaccine, which suggests that vaccination of pregnant women, particularly during a YF epidemic, may not be contraindicated.

Niedrig M et al: evaluation of an indirect immunofluorescence assay for detection of immunoglobulin m (IgM) and IgG antibodies against yellow fever virus. ***Clinical and Vaccine Immunology,*** **2008, 15: 177-181**

This study evaluated the first commercial indirect immunofluorescence assay (IFA) using Euroimmun Biochip technology for the serodiagnosis of immunoglobulin G (IgG) and IgM antibodies against yellow fever virus (YFV) and compared it with the plaque reduction neutralization test (PRNT). Analysis of 150 sera taken from individuals after vaccination with the 17D yellow fever vaccine established an overall correlation between the tests of 98.7%. The sensitivity and specificity, calculated using the 150 sera from vaccinees and 150 sera from healthy blood donors, were 95% and 95%, respectively, for the IgG IFA; and were 94% and 97% respectively for the IgM IFA. Antibody titres found using the PRNT correlated poorly with the IgM and IgG titres detected by IFA. The analysis of preexisting heterologous flaviviral immunity revealed the presence of antibodies reactive with YFV, tick-borne encephalitis virus, West Nile

virus, Japanese encephalitis virus, and dengue virus serotypes 1 to 4 in 20 out of the 150 vaccinees. The indirect IFA showed that nine individuals with previous flaviviral exposure who received 17D vaccine failed to produce detectable IgM antibodies. Despite this preexisting immunity, all vaccinees developed protective immunity as detected by PRNT and anti-YFV IgG antibodies as detected by IFA. The high specificity and sensitivity of the IFA make it a useful tool for rapid diagnosis of yellow fever during outbreaks, for epidemiological studies, and for serosurveillance after vaccination.

Nishioka SA et al: Yellow fever vaccination during pregnancy and spontaneous abortion: a case-control study. *Tropical Medicine & International Health*, 1998, 3 (1):29–33.

This study investigated the possible association between Yellow fever (YF) vaccine (inadvertently) administered during early pregnancy and spontaneous abortion. A hospital-based case-control study was conducted in a Brazilian town after a YF vaccine campaign that followed an epidemic of dengue. The study included 39 women who attended a university hospital with spontaneous abortion (cases) and 74 pregnant women attending the antenatal clinic of that hospital (controls). The crude odds ratio (relative risk estimate) of this association was 2.49, which dropped to 2.29 (95% CI 0.65–8.03) when adjusted for several confounders by multiple logistic regression. Dengue and exposure to organophosphate insecticide fogging during pregnancy were not associated with spontaneous abortion. This study, although small, provides some evidence that women vaccinated with YF vaccine during early pregnancy have an increased risk of having spontaneous abortion. Based on these findings, a sensible recommendation would be to avoid YF vaccination of pregnant women unless their risk of acquiring YF outweighs the risk of vaccine-related abortion.

Roukens et al: Elderly subjects have a delayed antibody response and prolonged viraemia following yellow fever vaccination: A prospective controlled cohort study. PLoS One, 2011, 6(12): e27753

Yellow fever vaccination (YF-17D) can cause serious adverse events (SAEs) but the mechanisms involved are poorly understood. Older age has been identified as a risk factor. This study tested the hypothesis that the humoral immune response to yellow fever vaccine develops more slowly in older than in younger subjects. Young volunteers (18–28 yrs, N = 30) and elderly travellers (60–81 yrs, N = 28) were vaccinated with YF-17D and their neutralizing antibody titres and plasma YF-17D RNA copy numbers were measured before vaccination and at 3, 5, 10, 14 and 28 days after vaccination. Ten days after vaccination, seroprotection was attained by 77% (23/30) of the young participants and by 50% (14/28) of the elderly participants ($p = 0.03$). Accordingly, the geometric mean titre (GMT) of the younger participants was higher than that of the older participants. At day 10 the difference was +2.9 IU/ml (95% CI 1.8–4.7, $p = 0.00004$) and at day 14 +1.8 IU/ml (95% CI 1.1–2.9, $p = 0.02$, using a mixed linear model. Viraemia was more common in the older (86%, 24/28) than in the younger participants (60%, 14/30) ($p = 0.03$) with higher YF-17D RNA copy numbers in the older participants. Older subjects (aged over 60) had a delayed antibody response and higher viraemia levels after primary yellow fever

vaccination. We postulate that with older age, a weaker immune response to yellow fever vaccine allows the attenuated virus to cause higher viraemia levels which may increase the risk of developing SAEs. This may be one piece in the puzzle of the pathophysiology of YEL-AVD.

Suzano CE et al: The effects of yellow fever immunization (17DD) inadvertently used in early pregnancy during a mass campaign in Brazil. ***Vaccine,*** **2006 24(9):1421-1426**

This study describes inadvertent immunization of pregnant women during a mass vaccination campaign in the Campinas region of the state of São Paulo, Brazil, in February-March 2000. Pregnant women who received the YF vaccine were identified at primary health clinics and referred to the study site, a reference centre serving 42 towns in a region with a population of 3,000,000. A 12-month serological follow-up for newborns (PRNT), and an examination to detect congenital abnormalities was offered to pregnant women, who signed a consent form. In a sub-sample of women who were delivered at the study site, additional exams were proposed: neonatal fontanel ultrasound, funduscopy, audiometry, neuro-paediatric follow-up to 12 months of age, and IgM detection at birth. Fifteen blood samples from placentas and umbilical cords were tested for PCR. A total of 480 pregnant, immunized women who had received the vaccine at a mean of 5.7 weeks (95% CI 5.2–6.2) of gestation were identified. Most were unaware of their pregnancy at the time of vaccination. Only 46.7% were counselled to avoid immunization if pregnant. After a minimum 6-week interval, 98.2% pregnant women were IgG positive. A total of 19.6% of women reported mild adverse events (headache, fever or myalgia). No IgM antibodies were detected at birth and no placental or umbilical cord blood was positive according to PCR. The frequency of malformations (2.3% or 7/304 babies), miscarriages (2.5% or 11/441 pregnancies), stillbirths (0.7%) and premature delivery (7.8%) was similar to that found in the general population. At 12 months follow-up, 7% of samples were reactive to PRNT. However, after 12 months, only one child was seropositive. Contrary to a previous study, maternal seroconversion was very high when immunization was carried out in early pregnancy. Vaccine applied during the first trimester does not appear to cause malformations, complications to the central nervous system, nor adverse perinatal results as represented by premature deliveries or perinatal deaths. The 12-month serological follow-up is inconclusive and should be extended to 24 months. Evaluation of the risk of miscarriage was hindered by late presentation at the study clinic.

Veit O et al: Immunogenicity and Safety of Yellow Fever Vaccination for 102 HIV-Infected Patients. ***Clinical Infectious Diseases,*** **2009, 48 (5):659-666.**

Yellow fever vaccine (17DV) has been investigated incompletely in human immunodeficiency virus (HIV)-infected patients, and adequate immunogenicity and safety are of concern in this population. Using the Swiss HIV Cohort Study, were identified. 102 patients who received 17DV while HIV- infected had neutralization titres (NTs) analyzed using the plaque reduction neutralization test. NTs of 1:⩾10 were defined as reactive, and those of 1:<10 were defined as

nonreactive, which was considered to be non-protective. The results were compared with data for HIV-uninfected individuals. Serious adverse events were defined as hospitalization or death within 6 weeks after receipt of 17DV. At the time of 17DV administration, the median CD4 cell count was 537 cells/mm^3 (range, 11-1730 cells/mm^3), and the HIV RNA level was undetectable in 41 of 102 HIV-infected patients. During the first year after vaccination, fewer HIV-infected patients (65 [83%] of 78; P=.01) than HIV-uninfected patients revealed reactive NTs, and their NTs were significantly lower (P<.001) than in HIV-uninfected individuals. Eleven patients with initially reactive NTs lost these reactive NTs ⩽5 years after vaccination. Higher NTs during the first year after vaccination were associated with undetectable HIV RNA levels, increasing CD4 cell count, and female sex. No serious adverse events after 17DV administration were found. In conclusion, HIV-infected individuals responded to 17DV with lower reactive NTs, demonstrated non-protective NTs more frequently, and may experience a more rapid decline in NTs during follow-up. Vaccination with 17DV appears to be safe in HIV-infected individuals who have high CD4 cell counts, although serious adverse events (in up to 3%) cannot be excluded.

Veit O et al. Yellow fever vaccination in HIV-infected patients, *HIV Therapy*, 2010, 4, (1): 17-26

Millions of HIV-infected individuals are at risk of yellow fever (YF) and vaccination with the 17D YF vaccine is the most effective preventive strategy. Increased vaccine coverage campaigns, guided by the WHO, are being used to prevent outbreaks in YF-endemic countries, including HIV-endemic areas. Limited data on the safety and immunogenicity of 17D YF vaccine in HIV-infected individuals suggest a reduced immune response and good tolerance of the vaccine, but these data come from small studies, mainly in travelers with CD4 cell counts above 200 cells/ mm^3, . However, rare serious adverse events cannot be excluded. According to current recommendations, 17DV should only be given to asymptomatic HIV-infected individuals with a CD4 cell count above 200 cells/mm^3. Data concerning 17DV in HIV-infected individuals living in YF-endemic areas are missing, making mass immunization campaigns against YF very challenging. There is a need for further studies into the safety and efficacy of 17DV in HIV-infected individuals.

Yellow Fever Stockpile Investment Case. Submitted by the Yellow Fever Task Force to the Global Alliance for Vaccines and Immunization (GAVI) in December 2005.

This report describes the need for investment in a YF vaccine stockpile following a resurgence of yellow fever (YF), with an increase in reported urban outbreaks in West Africa in 2005. It argues that multiple outbreaks are likely to occur simultaneously in several places, undermining the response capacity of the country as well as the support capabilities of the international community. The risk of large and uncontrollable outbreaks in urban areas in Africa was very high, particularly among the 12 highest risk Global Alliance for Vaccines and Immunization (GAVI)-eligible countries. In 2005, an estimated 206,000 cases and 52,000 deaths occurred in these 12 countries and it is estimated 1.5–2.7 million deaths will occur in these countries.
The objective of the proposed investment is to control YF and reduce the risk of outbreaks through inclusion of YF vaccine in routine infant immunization programmes for infants aged 9

months, to implement preventive mass vaccination campaigns to rapidly increase population immunity in high-risk areas and to protect susceptible older age groups. When fully implemented (as in the case of the Gambia), this two-component strategy has proven to be highly sustainable and effective in reducing mortality and morbidity caused by YF.