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Serious adverse events associated with yellow fever vaccine

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Yellow fever vaccine was considered one of the safest vaccines, but in recent years it was found that it could rarely cause invasive and disseminated disease in some otherwise healthy individuals, with high lethality. After extensive studies, although some risk factors have been identified, the real cause of causes of this serious adverse event are largely unknown, but findings point to individual host factors. Meningoencephalitis, once considered to happen only in children less than 6 months of age, has also been identified in older children and adults, but with good prognosis. Efforts are being made to develop a safer yellow fever vaccine, and an inactivated vaccine or a vaccine prepared with the vaccine virus envelope produced in plants are being tested. Even with serious and rare adverse events, yellow fever vaccine is the best way to avoid yellow fever, a disease of high lethality and should be used routinely in endemic areas, and on people from non-endemic areas that could be exposed, according to a careful risk-benefit analysis.

Keywords: disease, neurotropic disease, serious adverse events, vaccine safety, yellow fever vaccine

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Introduction

Yellow fever vaccine (YFV 17D) is a landmark on vaccine history. Without it, life in the tropics would be extremely difficult, due to its direct effect, a serious disease of high lethality, and indirect effects, due to its psychological and social effects – terror of disease – compromising commerce with foreign countries, occupation of territory and economic development. Clearly, a vaccine was needed. In 1932 Andrew Sellards, from Harvard University, and Jean Laigret, from the Pasteur Institute,[1] developed the so called French vaccine, which was too neurotropic, and recognizing this, Max Theiler, who had participated on the development of the French vaccine, developed a new vaccine strain, 17D, which was much less neurotropic. Extensive clinical trials in Brazil showed it was immunogenic and safe,[2] and Max Theiler received the Nobel Prize for this achievement.

Problem with safety reappeared in the form of jaundice, which was shown to be associated to the use of human serum during vaccine preparation of subjects infected with hepatitis virus.[3] This observation led to a serum-free vaccine.[4] Neurotropism was also noted in mass vaccination campaigns,[5] as well as variations in immunogenicity, and the concept of seed lot was established to reduce production variables. Even so, cases of encephalitis still occurred in very young children, so the inferior limit for use of yellow fever vaccine was established at 9 months of age, or not less than 6 months in epidemic situations, and encephalitis cases were reported only rarely ever since. It became widely accepted after decades of use of the YF 17D vaccine that it was generally safe with few and transient[6] adverse reactions and was for many years considered one of the safest vaccines available.

Vaccine-Associated Viscerotropic Disease (YEL-AVD)

It was a shock when several cases of visceral dissemination of YFV 17D virus were reported, with high lethality, with the United States and Brazil[7,8] being the first countries to identify the new syndrome. The clinical picture is similar to wild yellow fever.[9] Causal relationship to YFV 17D virus was established beyond doubt, and a search for possible explanations

followed, but until now without success. The limited number of genetic variations in the genome of the vaccine viruses and the lack of consistency of these changes when the genomes of case viruses are compared do not support single site reversion to wild type virus sequence, and therefore cannot explain the clinical picture.[10]

All cases are first-time vaccinees. One underlying risk factor for YEL-AVD is thymectomy,[11] and old age also seems to be important, but evidence is conflicting across studies. One of the main difficulties is that the number of cases of serious adverse events is small, so it is not possible to reach statistically-based conclusions. For example, in Brazil, considering probable (6) and confirmed (10) cases, according to CDC criteria, the age distribution is depicted in **Table 1**.

There are also large differences in reporting rates according to regional or epidemiological peculiarities or quality of the surveillance system.[12] In a study of adverse events during a campaign in Argentina,[13] there was one YEL-AVD confirmed case per 1,943,000 doses administered (0.05/100,000 doses). Including 12 probable cases, the rate increased to 0.6/100,000 doses, 7/12 were in people >50 years old (but risk per age group is not provided), and 9/12 were male. Rafferty et al.[14] in a systematic review, found that 2 out of 5 studies showed significantly higher rate of YEL-AVD among the elderly population, and considered that this population may be at increased risk of YEL-AVD, but the evidence was limited. Seligman showed suggestive evidence of increased risk of YEL-AVD in young women without known immunodeficiency.[15]

One of the Brazilian YFV 17D-AVD cases was in a 19 year old woman, who died. Her sister, when she was 12 years of age, had also a serious adverse event after YFV 17D vaccination, suggestive of YEL-AVD, but recovered. Her aunt had systemic lupus erythematosus (SLE). Two brothers, of 30 and 34 years of age, both with Addison's disease and receiving physiological doses of cortisone, died with probable YEL-AVD. These cases suggest that there could be a genetic predisposition to YEL-AVD. Genetic studies in cases and relatives of patients could perhaps uncover some genetic traits associated with YEL-AVD. In one well studied case there were minor genetic variations on the genes for OAS1 and OAS2[16] that could be responsible for the high virus levels, and this issue should be explored further. In another case,[17] anomalies in the innate immune response with possible disruption of the CCR5-RANTES axis were found. Such breakdown could impair migration of monocytes to sites of infection in tissues, with a milder innate response failing to limit early viral replication although the mounting of adaptive immune response was adequate. A depressed monocyte cytokine synthesis was found by our group in a case with a mixed pattern of viscerotropic and neurotropic disease, in a patient with SLE.[18] Strong responses in both cell-mediated and humoral responses were found in these cases and also in a fatal case in Spain.[19] As a rule, neutralizing antibody titers are high in YEL-AVD, and taken together these findings point to defects in innate response in YEL-AVD cases. Coherent with this view, the symptoms of YEL-AVD begin at a short time after vaccination in most cases.

Vaccine-Associated Neurotropic Disease (YEL-AND)

The frequency of neurologic events after YFV 17D vaccination was also uncovered.[20] It became clear that YEL-AND cases occur several days or weeks after vaccination. Rates during a campaign in 2009 in RS (Rio Grande do Sul State) with enhanced passive surveillance were much higher than with the routine passive surveillance in the rest of Brazil.[21] The overall rate of neurotropic disease per 100,000 doses in RS was 1.03, higher than expected. In RS the highest risk was for the age group from 5 to 9 years, but again confidence intervals for RRR were wide. Although prognosis of these cases is generally good, there is reason for concern. It should be noted that with the French vaccine, no longer in use, the rate of postvaccinal encephalitis was 3–4% in children, with few cases in adults,[22] and with a neurotropic lot of 17D vaccine, used at the beginning of production of 17D vaccine, the rate was also higher in children from 5 to 14 years than in older adolescents and adults.[5] Two well documented cases of neurotropic disease in newborns acquired through breast-feeding on lactating mothers vaccinated against yellow fever were reported in RS.[23,24]

Risk Factors

Thomas et al made a systematic review of studies evaluating risk factors for serious adverse events after YFV 17D, including use in pregnant women and HIV positive individuals.[25] The rarity of events precludes definitive conclusions, but the YFV 17D vaccine seems to be safe in pregnancy and in HIV positive individuals who are not overly immunodeficient, with >200 cells/mm^3, and CDC considers that YFV 17D may be administered if CD4 count is ≥500/mm^3, or ≥25% of total lymphocytes for children aged <6 years.[26-28]

Table 1. Viscerotropic disease (YEL-AVD) probable and confirmed cases and reporting risk ratio (RRR) by age group, Brazil, 2007–2012*

Age group years	Vaccine first doses	YEL-AVD N	Rate 100,000 doses	RRR (95% CI)
<1	8,442,107	1	0.01	0.19 (0.02; 1.44)
1–4	2,222,775	3	0.13	2.10 (0.58; 7.65)
5–9	1,079,662	0	0.00	undef
10–14	1,928,089	0	0.00	undef
15–59	15,592,430	10	0.06	Ref
60+	2,169,568	2	0.09	1.44 (0.31; 6.56)
Total	31,434,631	16	0.05	

Ref = Reference; Undef = Undefined.
*The Brazilian immunizations program provides the number of doses administered per age groups, and discriminates first doses and boosters Confidence intervals for RRRs are not statistically significant. Six cases were in males and 10 in females.

What about autoimmunity? This issue has been raised several times by us and others[12,26] as many cases have a personal history of autoimmune diseases, such as SLE, thyroid disorders, Addison's disease, gastrointestinal autoimmune diseases, etc. It should be noted that thymectomy for thymomas or myasthenia gravis are associated with autoimmunity,[29] so the recognized risk factor for thimectomy could be part of a spectrum of risk associated with autoimmune diseases. This possibility should be further investigated, and some speculative hypotheses could be explored, such as cross reaction of preformed antibodies of individuals with autoimmunity with vaccine virus, formation of immune complexes, and antibody enhancement.

Seligman evaluated risk factors for YEL-AVD, and found that there was statistical support for considering risk groups elderly males, women between the ages of 19 and 34, people with a variety of autoimmune diseases, and individuals who have been thymectomized because of thymoma.[30]

Vaccine Virus

With the first viscerotropic cases there was an extensive search for YF 17D virus mutations that could explain the adverse event. In one exhaustive study done by our group, nucleotide sequencing of viral genomes from 2 fatal cases revealed minor variations at some nucleotide positions when compared to the secondary seed lot (102–84) virus used to produce the respective vaccine lots, and did not result in amino acid substitutions. Intracerebral and intrahepatic inoculation of rhesus monkeys with YFV 17D viruses isolated from the 2 patients caused minimal viremia and no indication of increased virulence. So, it was concluded that the most probable explanation was individual susceptibility due to some unknown host factor.[10] The most baffling event was a cluster in space and time of 5 cases of YEL-AVD in Peru, of which 4 were confirmed cases, with the same lot, and intensive investigation yielded no abnormalities of the implicated vaccine lot and no common risk factors.[31] By now, there is no conclusive evidence that demonstrates that YEL-AVD is caused by increased virulence due to mutations in the genome of the YF 17D vaccine virus.[26]

Virus Dose

It has been known for a long time that YFV 17D vaccine could be used in much lower doses than the usual dose. There is no maximum dose requirement for yellow vaccine production. One hypothesis for YEL-AVD was that high doses could be implicated, but there is no indication of that. In a dose-response study viremias by virus isolation, qRT-PCR, and clinical reactogenicity were statistically similar across the different study arms, with de-escalating doses from 27,476 IU (approximately 52,000 PFU, the usual dose) to 31 IU (approximately 60 PFU)[32] Mass vaccination campaigns include errors administering vaccines in doses from 10 times to 25 times the recommended dose (n = 163), but there were no serious adverse events.[13,33,34] Moreover, in Bio-Manguinhos/Fiocruz, the release titers are verified for all lots and have been around 70,000 PFU/human dose and within narrow limits of variation across different lots along the last decades, showing a very consistent and homogeneous production. So, this hypothesis seems untenable.

Viremia as a Determinant of Serious Adverse Reactions

We do not know what the normal biodistribution of vaccine virus or virus fragments after vaccination in normal vaccinees is. There are evidences that vaccine virus may persist for a long time after vaccination. In our dose-response study, viremias (by real time RT-PCR) were found until 36 days after vaccination. Recent studies report frequent (44%) or prolonged (until 198 d) shedding of vaccine RNA in urine of vaccinated individuals.[35–36] Moreover, the elderly may also have prolonged viremia after vaccination with YFV 17D virus.[37] So, it would be no surprise if some tissues also have RNA positivity for a long time after vaccination. The Brighton definition correctly requires that besides RNA positivity in tissues, there should be characteristic histopathology (eg, liver midzonal necrosis, Councilman bodies) for confirmation of YEL-AVD. However, this definition includes positivity of viremias by RT-PCR $\geq$ 14 days after vaccination as one criterium for confirmation of YEL-AVD,[38] which could inflate this diagnosis.

The Influence of Flavivirus Heterologous Immunity on Human Vaccination with YF 17D Virus

We found in our dose-response study that YF 17D viremias were much less frequent in dengue-seropositive individuals, as measured by viral plaquing. In Ecuador, it was found that previous dengue infection decreased the severity of wild yellow fever.[39] This is in line with an experimental study in monkeys by Theiler & Anderson, who found that dengue-immune monkeys had lower viremias and relative resistance to yellow fever virus.[40] In South East Asia, endemic for dengue and Japanese encephalitis (another flavivirus), there is no yellow fever, and one possible explanation is cross-protection afforded by the immune response to dengue (and JE) virus infections. Theoretically, dengue infections could decrease the frequency of serious adverse events after vaccination, due to lower viremias.

In yellow fever endemic areas the frequency of serious adverse events is much lower.[12,41] One possibility is that mothers immune to YF through exposure to wild virus or vaccination could protect their children by passive transmission of antibodies, so lowering adverse events when vaccination starts at 9 months of age. Also, in YF endemic areas, people of African descent predominate, and this population may have been selected for resistance to YF,[42] and possibly to YF 17D virus invasiveness. In Brazil skin color of vaccinees and cases has not been recorded but most YEL-AVD cases occurred in parts of the country in which caucasian population predominates.

Perspectives

Efforts are being made to develop a new YF vaccine that could avoid serious

adverse events. One approach is using inactivated YF 17D virus, which showed good immunogenicity in pre-clinical and clinical studies[43]; and we are also following this trend by producing the Envelope E protein in plants, in collaboration with the Fraunhofer Institute in the US. Some challenges being tackled at this stage are the improvement of antigen expression and the study of its immunogenicity using new adjuvants.

Conclusion

We do not know as yet, what mechanism(s) of host and YF 17D leads to serious adverse events (YEL-AVD or YEL-AND). Although some risk factors are proposed, the rarity and unpredictability of these events are an obstacle for their investigation. Protocols for investigation have been developed,[44] and should be applied with strict adherence to collection, transport and delivery of biological samples to the laboratories in good conditions. Even with these serious adverse events, yellow fever vaccine is the best way to avoid yellow fever, a serious disease of high lethality, and should be used routinely in endemic areas, and on people from non-endemic areas that could be exposed according to a careful risk-benefit analysis.[45]

Disclosure of Potential Conflicts of Interest

All authors work for Bio-Manguinhos/Fiocruz, a government non-profit producer of vaccines, including the yellow fever vaccine.

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