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## **Travel medicine : knowledge, attitude, practice and immunisation**

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### **Citation**

Roukens, A. H. E. (2010, March 4). *Travel medicine : knowledge, attitude, practice and immunisation*. Retrieved from <https://hdl.handle.net/1887/15037>

Version: Corrected Publisher's Version

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**Note:** To cite this publication please use the final published version (if applicable).

## **Reduced intradermal test dose of yellow fever vaccine induces protective immunity in individuals with egg allergy**

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*Vaccine. 2009; 27:2408-9*

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## **Abstract**

### ***Background***

Persons with a history of egg allergy are susceptible to developing a strong urticarial or anaphylactic reaction to the yellow fever vaccine. Therefore, in these persons a test dose (1/5th of the conventional dose) is administered intradermally, in order to monitor the local skin reaction.

### ***Methods***

The neutralising antibody response after the yellow fever vaccine (YF-17D) skin test was measured in 7 egg allergic persons in whom further vaccination was abandoned because of a strong local urticarial reaction to the YF-17D vaccine test dose.

### ***Results***

We found that this test dose of 0.1 mL of YF-17D vaccine was sufficient to induce a protective antibody response in all 7 subjects.

### ***Conclusion***

Intradermal injection of 1/5th dose of the yellow fever vaccine appears to be sufficient, in non-allergic as well as allergic persons, and non-inferior to the subcutaneous full dose.

## Introduction

The yellow fever vaccine is considered to be one of the most effective and safe vaccines since its development in the 1930's. Mild adverse reactions such as low-grade fever, myalgia, and local redness or tenderness at the site of injection occur in 10-30% of vaccinees, 2 - 6 days after vaccination [1]. More serious adverse events, such as yellow fever vaccine-associated neurotropic disease (YEL-AND) or viscerotropic disease (YEL-AVD), have been reported, but are very rare (0.3-0.4 per 100.000 administered doses) [2]. In addition to these adverse events that are typically related to viral replication, anaphylactic reactions probably triggered by the hydrolysed porcine gelatin or egg proteins present in the vaccine, have been reported with a risk of 0.8 per 100.000 doses [3].

Because the yellow fever 17D vaccine strain (YF-17D) is propagated on embryonated chicken eggs, a history of acute hypersensitivity to eggs or egg products is a contraindication to vaccination. If a subject with a probable history of egg allergy is planning on traveling to an area with a significant risk for contracting yellow fever a test dose of the vaccine can be given under close medical supervision. According to the Dutch guidelines of the National Coordination Centre for Travelers' Health a test dose of 0.1 mL of YF-17D vaccine (1/5<sup>th</sup> of the normal vaccine dose) is administered intradermally, and a control dose of 0.1 mL physiologic saline (0.9% NaCl) is injected intradermally in the contralateral arm [4]. The test is read after 30 minutes. If the diameter of the cutaneous wheal of the test dose is less than 2 times the diameter of the saline control, the skin test is considered negative and the remaining 0.4 mL of vaccine is administered subcutaneously. In case of a positive skin test, further vaccination is abandoned [4].

In 1943, Fox and colleagues observed a protective immune response after intradermal administration of the YF-17D vaccine [5]. However, the population investigated was small and the methods used to assess antibody responses are irreconcilable with current definitions of seroprotection as formulated by the WHO. We have recently shown that intradermal vaccination with 0.1 mL YF-17D vaccine induced protective neutralising antibody levels in healthy volunteers [6]

To ascertain this protective response also occurs after the YF skin test in egg allergic individuals, we measured the neutralising antibodies in 7 persons in whom further vaccination was abandoned because of a strong local urticarial reaction to the YF-17D vaccine test dose.

## Methods

Serum samples of immunocompetent individuals who had received the yellow fever vaccine test dose in our hospital since 2000 (start of registration), and who developed a positive skin reaction were tested. Serum of 7 of 11 registered patients with a positive skin test could be obtained. The live, attenuated, YF-17D vaccine that was used (Arlivax®, Medeva, Belgium, or Stamaril®, Sanofi Pasteur, France) was stored according to manufacturer's guidelines. Administration of the test dose (performed as described previously [6]) and close medical observation of the subjects was performed at the outpatient travel clinic of the Leiden University Medical Centre (LUMC). One individual was hospitalised for observation during the procedure because of the anticipated risk of anaphylaxis.

Neutralising antibodies were measured by constant virus – varying serum dilution Plaque Reduction Neutralisation Test (PRNT), using a slightly modified technique originally described by De Madrid and Porterfield [7]. Briefly, sera were complement inactivated at 56°C for 1 hour. Postvaccination sera were tested in two-fold dilutions starting from 1:16 to 1:512. One hundred Plaque Forming Units (PFU) of YF-17D virus were added to each serum dilution. All test sera were assayed in duplicate in 6-well plates. Virus neutralisation (VN) was calculated for each serum dilution (i) according to the following formula:  $VN(i) = 100 - (\text{number of PFU in diluted postvaccination serum} / \text{number of PFU in medium}) * 100$ . The highest serum dilution at which at least 80% virus neutralisation occurred (a  $\log_{10}$  neutralisation index of 0.7) was taken as endpoint, as this corresponds to the generally accepted definition of protection [8]. A reference serum, obtained from the National Institute for Biological Standards and Control (<http://www.nibsc.ac.uk/>) was used for quantification of the antibody response in International Units per milliliter (IU/mL). In our hands a 0.7 log<sub>10</sub> plaque reduction in 1:10 diluted serum corresponds to a titre of 0.5 IU/ml [95%CI 0.3 – 0.8 IU/ml] (unpublished data). Similar values have been found by others [9].

## Results

The characteristics of the vaccinated individuals, their skin reaction and antibody response to the vaccine test dose are given in table I. Similar to our findings in healthy volunteers, we found that the test dose of 0.1 mL of YF-17D vaccine was sufficient to induce a protective antibody response in all 7 subjects with egg allergy (Table 1), with a mean concentration of 5.3 IU/ml [99% CI 2.0-8.6 IU/ml]. No adverse reactions

**Table 1** Characteristics of egg-allergic persons and outcome of test dose vaccination

N	Age (yrs)	Sex	YF vaccine <sup>a</sup>	Year vacc	Wheal control (mm)	Wheal test dose (mm)	Time vacc serology <sup>b</sup> (wks)	Serum dilution VN80% <sup>c</sup>	Calculated serum dilution VN80% <sup>d</sup>	IU/ml <sup>e</sup>
1	17	F	A4AO55AC	2000	7	16	9	1:16	1:30	1.5
2	20	M	A 510494	2003	5	35	5	1:128	1:245	11.7
3	1	M	A 763219	2003	4	16	3	1:128	1:145	6.9
4	28	F	A 763219	2004	0	15	8	1:32	1:55	2.6
5	26	F	A 763219	2004	7	30	4	1:64	1:110	5.3
6	53	M	A 765135	2005	7	32	5	1:64	1:115	5.5
7	2	M	S A5323	2007	6	13	32	1:64	1:70	3.3
Mean										
[99%CI]										5.3 [2.0-8.6]

<sup>a</sup> YF = yellow fever, A = Arlivax, S = Stamaril.  
<sup>b</sup> Time vacc serology is the time between test dose administration and serology.  
<sup>c</sup> Serum dilution VN80% is the highest serum-dilution at which at least 80% VN occurred. VN = virus neutralisation in plaque reduction neutralisation test.  
<sup>d</sup> Calculated serum dilution was the exact graphical serum dilution at which 80% VN occurred.  
<sup>e</sup> IU/ml was calculated with the calculated serum dilution VN80%, according to the reference serum (143 IU/ml, VN80% at serum dilution 1:3000).  
CI = Confidence Interval.

additional to the local wheal formation were observed in the individuals at the outpatient clinic. The hospitalised patient developed a sensation of swelling of the tongue that responded to treatment with antihistamines.

## **Discussion**

Travellers with egg allergy in whom vaccination was abandoned after the YF-17D test dose are very likely protected by the test dose. Apparently, the wheal-and-flare formation within 30 minutes after vaccine administration did not affect the formation of neutralising antibodies against yellow fever virus. The effect of mast cell degranulation on viral entry and replication remains unknown and could be important for the response to intradermal yellow fever vaccination. It has been shown recently that locally activated mast cells can actually enhance the immune response to a vaccine antigen [10].

Although all 7 egg allergic individuals were protected against yellow fever, the sample size of this study is too small to conclude that documentation of this protection by virus neutralisation test is no longer needed. Post-vaccination testing would no longer be required if 100% success rate of intradermal test dose vaccination would be achieved in 72 egg allergic individuals, corresponding to the lower boundary of the 95% confidence interval of the percentage of individuals who should be protected after YF-17D vaccination according to the WHO. In conclusion, these results show that, similar to healthy (non-allergic) individuals [6], subjects with a history of egg allergy in whom an intradermal test dose of 0.1 mL YF–17D vaccine yielded a strong local urticarial reaction, are able to develop a protective immune response and do not need further vaccination.

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