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Perspective

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Yellow fever vaccination for immunocompromised travellers: unjustified vaccination hesitancy?

Wesley de Jong, MD[1,*], Prof. Rob A. de Man, MD, PhD[2], Virgil A.S.H. Dalm, MD, PhD[3], Chantal B.E.M. Reusken, PhD[1,6], Marco Goeijenbier, MD, PhD[1,4], and Prof. Eric C.M. van Gorp, MD, PhD[1,5]

[1]Department of Viroscience, Erasmus University Medical Center, 3015 GD Rotterdam, The Netherlands, [2]Department of Gastro-Enterology and Liver Diseases, Erasmus University Medical Center, 3015 GD Rotterdam, The Netherlands, [3]Department of Internal Medicine, Division of Clinical Immunology and Department of Immunology, Erasmus University Medical Center, 3015 GD Rotterdam, The Netherlands, [4]Department of Internal Medicine, Erasmus University Medical Center, 3015 GD Rotterdam, The Netherlands, [5]Department of Infectious Diseases, Erasmus University Medical Center, 3015 GD Rotterdam, The Netherlands and [6]Netherlands Centre for Infectious Disease Control, National Institute for Public Health and the Environment, 3721 GM Bilthoven, The Netherlands

[*]To whom correspondence should be addressed. Email: w.dejong.2@erasmusmc.nl

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The evolution of treatment strategies has reduced the burden of disease, and for many people, the resulting improved quality of life has opened up travel opportunities. The necessary preparations for such travel often include getting vaccinated against a number of infectious diseases. However, for the immunocompromised traveller, live-attenuated vaccines, such as the YF vaccine, are usually contraindicated, because the health benefits usually do not outweigh the safety profile offered by the vaccination. Given that the principle 'first, do not harm' prevails, travel medicine guidelines dictate that live-attenuated vaccines should not be administered to such patients[1]. Instead, travel to YF-endemic countries is discouraged. This standpoint changes, however, when such a patient plans to travel frequently to an endemic region or intends to emigrate to one. In some cases, reasons such as family matters, job opportunities or work obligations leave little room for a change of plan. There is limited evidence that demonstrates that the YF vaccine may be adequately tolerated by immunocompromised patients and will induce the formation of antibodies in them[2].

Outbreaks and sporadic cases of YF in humans can occur, and these outbreaks can have a huge impact on a region and on global resources. For example, mass vaccination campaigns to protect people against YF can be implemented in regions in which the vaccination was previously not recommended or in which vaccine coverage was below the herd immunity target threshold. Frequent travel or emigration to such a region would put unvaccinated immunocompromised hosts at risk of contracting YF. Repeated requests by two patients made us re-evaluate the considerations described above, particularly bearing in mind that vaccination is the most effective way of combatting YF.

Patient A is a 25-year-old male who underwent liver transplantation, for which he uses tacrolimus (Advagraf), 5 mg q.d. His employer, a shipping company, wanted him to be vaccinated against YF. Given that he frequently visited YF-endemic regions in both South America and Central/West Africa, we considered it a potential health risk for him to travel unvaccinated. He was informed about the characteristics of the YF vaccine and the risks that vaccination would expose him to while using immune-suppressive therapy. Azevdo *et al.*[3] published case series of YF-vaccinated patients using lower to similar dosages of tacrolimus. Based on the work of Visser *et al.*[4], having reviewed the SmPC of tacrolimus and after consulting a senior infectious diseases specialist, an immunologist and a hospital pharmacist, we adjusted the tacrolimus dosage to 3 mg. After 7 days (doubled half-life of tacrolimus), the patient was vaccinated with Stamaril (live-attenuated 17D-204 YF vaccine, according to the manufacturer's specifications). The patient reported no complaints of reduced well-being. Moreover, after taking the patient's temperature twice a day for 14 days after the vaccination, no fever was detected. Using real-time reverse transcription polymerase chain reaction,[5] no viral RNA was detected on Days 3, 7, 14 and 21, post-vaccination. No changes were observed in routine haematology and chemistry laboratory tests. Twenty-one days post-vaccination, using Indirect Fluorescent Antibody

(IFA) assay, we detected IgG antibodies, which persisted for at least 325 days post-vaccination. Using a Virus Neutralisation Test (VNT), neutralizing antibodies to the 17D-204-vaccination strain were detected on Days 14 and 21 (1:102 and 1:203, respectively).

Patient B is a 35-year-old female. Since the age of 10, she has been followed at outpatient clinics for Sjögren's syndrome, secondary to a systemic lupus erythematosus. Recently, pulmonary involvement, including pleurisy and intra-pulmonary lesions, became apparent so she was initially treated with high-dosage steroids, followed by maintenance therapy with mycophenolic acid (CellCept) 1500 mg b.i.d. Her treating immunologist considered giving her YF vaccination because her studies required that she do internships in Central and West Africa. Furthermore, she would have to travel to these regions on a more frequent basis during future jobs. Given that YF continues to affect people in several regions of Africa,[6] the treatment team concluded that she was exposed to a real risk of contracting YF in future. CellCept has a non-competitive and reversible effect on lymphocyte function and a relative short half-life of less than 24 hours. With an estimated 5 days of immunosuppressive effect[4] and in the absence of disease activity, her treatment was interrupted for 14 days and she was vaccinated with Stamaril. During follow-up, we observed no signs of relapse of disease activity, both clinically and biochemically. Furthermore, no vaccination-related complaints were observed up to 14 days after vaccination. In blood collected on Days 4, 7, 11, 18, 25 and 46, we were not able to detect viral RNA nor IgG antibodies by an IFA (see above). However, using VNT, we found neutralizing antibodies on Day 46 (1:40). Due to an increase of the symptoms related to her known disease, treatment was restarted 4 weeks after vaccination.

About 15% of YF-infected individuals develop YF intoxication, which is characterized by remitting fever and organ failure, ultimately culminating in multi-organ failure. The limited treatment options that are available are a major reason for the 20–50% fatality rate in this group.[7] While healthcare professionals should follow the principle of 'first do not harm'[1] and advise immunocompromised patients to consider changing their travel destination, we encourage these professionals to rethink this position. The YF vaccines that are currently available are based on the attenuated 17D strain and are typically safe and effective.[2] About 600 million people have been vaccinated with them worldwide. Cases of neurotropic and viscerotropic disease (YEL-AND and YEL-AVD, respectively) after vaccination have been documented, but with incidence rates below 7 per 1 million vaccinations administered.[8] For known risk groups with a (relative) contraindication—such as babies <6 months, people with a thymus disorder, people aged ≥60 years, patients with multiple sclerosis or cellular or humoral immune disorders (e.g. using immunosuppressants) or human immunodeficiency virus-infected people with a CD4 count below 0.5×10^9/L—an increased risk of developing YEL-AND and YEL-AVD has been documented. However, conclusive statistics are lacking, due to heterogeneity and bias in different studies.

It is sometimes unclear which follow-up actions healthcare professionals should take when immunocompromised patients indicate that they intend to travel or emigrate to YF-endemic regions. It could be argued that issuing only the so-called 'waiver'—a document informing the immigration services of the country being visited that the patient cannot be safely vaccinated—is tantamount to sidestepping the responsibility of offering adequate protection to the travelling patient.

The vaccination of such patients against YF carries with it several risks. As mentioned previously, evidence of the safety and effectiveness (i.e. the development of neutralizing antibodies) of the vaccine is limited to systematic reviews of cases and expert opinions. In addition to the likelihood of developing neutralizing antibodies, the options for interrupting or reducing the immune-suppressive status of the patient should also be considered. The possibility of reducing the immune-suppressive status for safe and effective vaccination depends on the type of drug used, its dosage and the status of the underlying disease. Stopping or lowering medication in patients with an autoimmune disease may result in a flare-up, for example. Literature describing the successful administration of the YF vaccination—sometimes inadvertently—to immunocompromised patients is available.[9] The effective duration of the working of immune-suppressive medication has also been studied.[4] Based on these studies and our own observations it appears that there is some room for deviation from standard guidelines. It should be noted, however, that cases of a fatal outcome have also been documented.[10]

In our patients, the vaccination was safe and from the YF VNT it was evident that the patients' immune systems were able to produce neutralizing antibodies. The results obtained, however, do not guarantee sufficient protection against YF disease while travelling, because essential cellular responses that help to eliminate the virus can either be lacking or reduced.[4] Furthermore, the amount of long-term protection that is afforded remains unclear, as Lindsey *et al*. recently showed, e.g. that those with an immunocompromised condition were less likely to have YF-neutralizing antibodies in the long term. These patients are still at risk, and we must therefore repeat that, from a medical point of view, travel is not recommended.

We want to encourage healthcare professionals to not sidestep or 'waive' their responsibility of offering adequate protection to immunocompromised patients who frequently travel, or intend to emigrate to, (potential) YF-endemic regions. For these patients it is not enough to just sign the waiver that informs the immigration services. Instead, we advocate that that sparse literature that is available, together with their clinical experience, should be used to shift the balance and increase the number of YF vaccinations administered to individual immunocompromised patients intending to travel or emigrate to YF-endemic regions.

Preconditions for considering the YF vaccination of immunocompromised patients:

1. The patient should travel at least twice a year to a region that is considered to be at high risk for YF transmission (i.e. vaccination is strongly advised or mandatory by travel medication authorities and/or a YF outbreak or active virus transmission in humans is known for the region).
2. Travel to a YF-endemic region is unavoidable (i.e. family matters, work or study obligations).
3. The patient currently uses a single immunosuppressive agent.

If all of the above-mentioned preconditions apply, the following steps should be a literature and SmPC review and then consultation with the relevant specialists. After informed consent,

it may then result in the lowering or interruption of immunosuppressive therapy followed by the administration of the YF vaccination.

Author contributions

This manuscript was written by W.J. and co-authored by other authors mentioned at the beginning. Patients were referred by V.D. and R.M. Consultations at our travel clinic were performed by W.J. and supervised by V.D., R.M. and E.G. Sample analyses were supervised by C.R. All authors agree to submit this manuscript, and they have approved the final version.

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