Prescription of Yellow Fever Vaccine: The Experience of the International Vaccination Centre of the Loures-Odivelas Health Centre Group

Prescrição da Vacina Contra a Febre Amarela: Experiência do Centro de Vacinação Internacional do Agrupamento de Centros de Saúde Loures-Odivelas

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ABSTRACT

Introduction: Yellow fever is a vector-borne disease in sub-Saharan Africa and tropical South America regions which is preventable by an effective and safe vaccine. In some cases, it may cause serious adverse effects and should therefore be prescribed only to individuals at risk of exposure to the yellow fever virus or those traveling to countries requiring proof of vaccination. The aim of this study was to analyze the prescriptions of yellow fever vaccine, based on travel destination and type of referring consultation, according to the international recommendations of the World Health Organization.

Material and Methods: The database of the International Vaccination Centre of the International Vaccination Centre of the Loures-Odivelas Health Centre Group was used to analyze data concerning the year of 2016. Travelers who were prescribed and administered the yellow fever vaccine were grouped based on travel destination and type of referring consultation (travelers' medical consultations or non-specialist consultations).

Results: A total of 517 yellow fever vaccines were administered, with the highest proportion in female (53%) and in individuals aged 40 - 49 years (20.7%). One hundred and thirteen (22.6%) of the 499 individuals with known-destinations were travelling to non-endemic/non-epidemic countries and a greater proportion of those were prescribed in non-specialist consultations (27.3%) than in travel medicine consultations (8.8%).

Discussion/Conclusion: The highest percentage of yellow fever vaccines that were administered to individuals travelling to non-endemic/non-epidemic countries were prescribed in non-specialist consultations.

Keywords: Immunization Programs; Portugal; Travel; Yellow Fever Vaccine

RESUMO

Introdução: A febre amarela é uma doença de transmissão vetorial que ocorre na África Subsaariana e na América do Sul tropical, e é evitável por uma vacina eficaz e segura. Nalguns casos pode causar efeitos adversos graves, devendo ser prescrita apenas a indivíduos em risco de exposição ao vírus ou que viajem para países que exigem prova de vacinação. O objetivo deste estudo foi analisar a prescrição da vacina contra a febre amarela, de acordo com o destino da viagem e o tipo de consulta de referenciação, segundo as recomendações internacionais da Organização Mundial de Saúde.

Material e Métodos: Foi analisada a base de dados existente no Centro de Vacinação Internacional do Agrupamento de Centros de Saúde Loures-Odivelas, referente a 2016. Foram estudados os registos dos viajantes a quem foi prescrita e administrada a vacina contra a febre amarela, de acordo com o destino da viagem e o tipo de consulta de referenciação (consulta de medicina do viajante ou consulta não especializada).

Resultados: Foram administradas no total 517 vacinas contra a febre amarela, em maior proporção em indivíduos do sexo feminino (53%) e em indivíduos dos 40 aos 49 anos de idade (20,7%). Dos 499 indivíduos que tinham destino conhecido, 113 (22,6%) tinham como destino países não endémicos/não epidémicos, com uma maior proporção de prescrições em contexto de consultas não especializadas (27,3%) do que em consultas de medicina do viajante (8,8%).

Discussão/Conclusão: A maior percentagem de vacinas contra a febre amarela administradas a indivíduos que tiveram como destino países não endémicos/não epidémicos foram prescritas numa consulta não especializada.

Palavras-chave: Portugal; Programas de Imunização; Vacina contra Febre Amarela; Viagem

INTRODUCTION

Yellow fever (YF) is a viral disease transmitted to humans by an infected mosquito[1] and is endemic in some tropical and subtropical regions in South America and Africa. It is usually approached at a travel medicine outpatient clinic for patients travelling to countries from these geographical areas.[2] Yellow fever may be prevented with the eviction of the mosquito bite and with immunisation.[1]

According to the World Health Organization (WHO), the YF vaccine is recommended for all patients aged ≥9 months travelling to endemic regions, except patients with vaccine contraindications.[3]

The entry of travellers into a Member-State may depend on the presentation of a yellow fever vaccine certificate, due to issues regarding the control of vector-borne diseases, according to what has been established by the International Health Regulations approved by the member states of the

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WHO.[4] The vaccine may also be required for travellers coming from an area with yellow fever transmission, as established by the WHO, on entry into a non-endemic country where the vector is present.[4] A list of countries with risk of transmission and countries in which the YF vaccine is required is regularly updated by the WHO.

The YF vaccine is effective and safe and, from July 2016, a single dose has been recognized by the WHO as conferring life-long immunity.[1,5] Side effects are generally mild, even though severe adverse reactions may rarely occur, including allergic reactions, vaccine-associated neurotropic disease (including meningoencephalitis, Guillain-Barré syndrome and acute disseminated encephalomyelitis) and viscerotropic disease (frequently progressing to multiple organ failure).[6–8] Vaccine-associated neurotropic disease was primarily described in children aged <6 months.[3] A higher incidence of neurotropic disease has been found in patients aged 60 and older, associated to primary vaccination, according to a recent systematic review.[9] A 0.4 to 0.8 incidence rate per 100,000 doses distributed has been found.[6,10] Male patients aged 56 and over, young female, patients with autoimmune disorders and having undergone thymectomy due to the presence of thymoma are in higher risk of YF vaccine-associated viscerotropic disease[11] and a 0.3 incidence rate per 100,000 doses distributed has been found.[6,10]

The vaccine is contraindicated (absolute contraindication) in children aged < 6 months, patients with immune impairment, including impaired thymus function, symptomatic HIV infection or with CD4 cell count < 200/mL, primary immunodeficiency disorder, cancer or post-transplant immunosuppression, patients on immunosuppressive treatment or immunotherapy and in patients allergic to vaccine components (including eggs).[1] Relative contraindications exist in children aged six to nine months, pregnant or breastfeeding mothers and patients aged 60 and over.[1] Travel destination and travel type and conditions should be considered for the administration of the vaccine in these patients (for instance, an active disease has been reported at the travel destination, the patient is travelling within the rainy season or at the onset of the dry season or is travelling to jungle areas).[12] In case of contraindication, an adequately reasoned medical certificate and an International Certificate of Vaccination and Prophylaxis with an information of 'contraindication' should be required. This information should be considered by the authorities on arrival and the patient should be informed on this risk associated with non-vaccination.[4]

In Portugal, the YF vaccine can only be delivered at entitled yellow fever international vaccination centres.[4] Vaccine can be prescribed by any physician even though it should be prescribed at a travel medicine consultation by physicians frequently updating their knowledge on YF epidemiologic situation, following the most accurate recommendations and considering an approach to the other risks probably involved.[2,13] An inadequate approach to geography and epidemiology may lead to an over-exposure to vaccination as well as to unnecessary costs.[14,15]

An adequate health advice is crucial for a decline in the risk of travel-related infectious diseases.[16] An improved basic knowledge of travellers on malaria has been found in a Portuguese study on the quality assessment of a travel medicine clinic.[17] However, no further studies on this subject nor studies allowing for the comparison on the quality of travel health advice at a travel medicine consultation *vs.* a non-specialist consultation have been found. As regards the international overview, the prescription of the YF vaccine has been used as a parameter for the quality assessment of travel health advice.[16]

This study was primarily aimed at the analysis of the prescription of YF vaccine according to travel destination and outpatient referral, based on the WHO international recommendations.

The demographic characterisation of the population attending this international vaccination centre was the secondary endpoint of the study [patient's gender, age group and place of residence (healthcare centre cluster - *Agrupamento de Centros de Saúde (ACES)*].

MATERIAL AND METHODS

This was an observational, descriptive, retrospective study involving the analysis of the database of the no.13 International Vaccination Centre of the *ACES Loures-Odivelas*, including patient's gender, age, *ACES* corresponding to patient's place of residence, country of destination and administered vaccines between 1st Jan and 31st Dec 2016.

The YF vaccine is administered by a nurse at the no. 13 International Vaccination Centre to all the users with a medical prescription, regardless of their travel destination. Data on patients to whom the vaccine was prescribed and administered were analysed, based on the international recommendations for the prescription of the vaccine as regards the travel destination (YF endemic or non-endemic countries), according to outpatient referral (travel medicine or non-specialist consultation). The 2016 WHO list of countries with risk of YF transmission and countries requiring YF vaccination were used.[18]

Travellers to an YF non-endemic country to whom vaccine has been prescribed were subdivided according to the presence of the vector in the country of destination.

Travellers were subsequently divided by age group: 'Aged under 1 year', '1-59' and '60 or over' according to the YF vaccine relative contraindication ages.[1]

Unfilled records or 'different travel destination' responses were excluded from the analysis.

Data treatment and statistical analysis were carried out by the use of SPSS® (*Statistical Package for the Social Sciences*) *Statistics* 24.0 software. Chi-square test was used for the comparison regarding endemicity of the travel destination and outpatient referral, with a 5% significance level.

RESULTS

A total of 517 vaccines have been administered in 2016 at the no. 13 International Vaccination Centre [53% female patients, mostly 40-49 year patients (20.7%), mostly female

aged 20-29 year and male aged 40-49 year (Fig. 1)]. No vaccine has been administered to patients under the age of one and 64 patients (12.4%) were aged 60 and older (Fig. 1).

A percentage of 86% of the patients lived within the area covered by the *ACES Loures-Odivelas*, 13.4% in other municipalities within the Lisbon area and 0.6% elsewhere.

Only 25% of the patients were referred by a travel medicine clinic (18% of the patients had been referred by the own clinic, 4% by another travel medicine clinic within the public sector – National Health System - *Serviço Nacional de Saúde* (SNS) and 3% by a travel medicine private clinic). Most patients (75 %) were referred by a non-specialist clinic (64% of the patients by the outpatient clinic at the *ACES Loures-Odivelas*, 3% by other clinics within the SNS and 8% by a non-specialist private clinic).

A total of 18 medical records were excluded from the analysis due to a non-specified travel destination and 499 medical records have been studied. Vaccines were administered to patients travelling to an endemic country, a non-endemic country with the presence of the vector or to a country with no recommendation for the administration of the vaccine (Fig. 2).

A 91.2% rate of patients referred by a travel medicine clinic were travelling to an YF endemic country and 8.8% to a non-endemic country, even though with the presence of the vector (Table 1). A 72.7% rate of patients referred by a non-specialist consultation were travelling to an endemic country, 26.5% to a non-endemic country with the presence of the vector and 0.8% to a country with no recommendation for the vaccine (Table 1). Statistically significant differences were found between the endemicity of the country of destination and outpatient referral ($\chi^2 = 18.2507$; $p < 0.01$).

All patients aged 60 and older referred by a travel medicine clinic were travelling to an YF endemic country, while 84.4% of those referred by a non-specialist consultation were travelling to an endemic country and 15.6% to a non-endemic country with the presence of the vector (Table 2).

DISCUSSION/CONCLUSION

The YF vaccine is usually prescribed to patients travelling to tropical or subtropical regions and should be prescribed within a travel medicine consultation, involving recommendations aimed at the prevention of YF and other tropical or travel-associated diseases, through the identification of the risks associated to each destination and the analysis of the relationship between the risks and patients, tailored to each patient and to each destination.[1,2] The quality of travel health advice was also analysed.

In this study, only one in four patients was referred by a travel medicine clinic in 2016 and no data regarding other regions in Portugal were available for comparison. This rate can be explained by an increased search for medical advice, by the fact that a timely response was not always available within the Portuguese National Health System (SNS) or by a poorly disclosed service.[19] The quality of travel health advice is questionable in countries where the YF vaccine is prescribed by unexperienced physicians.[13]

According to the International Health Regulations, the YF vaccine is required to travellers to countries in which YF is not an endemic disease in some specific situations: patients coming from an YF endemic country (which is not the case of Portugal) or on transit at an airport coming from an endemic country. The absence of records on airport transit is one of the limitations of this study, which may explain the prescription of the vaccine for patients travelling to non-endemic countries, in addition to the shift of a country's epidemiological situation, requiring for a continuous knowledge update. In this study, a higher rate of patients travelling to YF non-endemic or intermittently epidemic countries has been found in those referred by non-specialist consultations, possibly due to the lack of updated knowledge. There are other

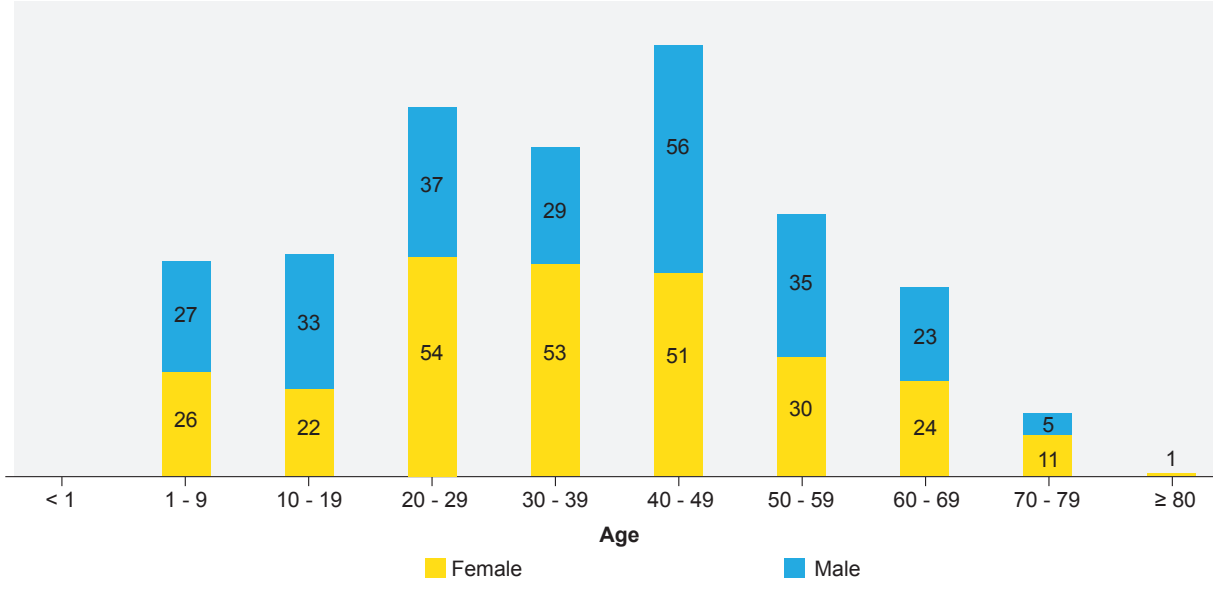

Figure 1 – Number of YF vaccines administered at the no. 13 International Vaccination Centre in 2016, according to patient's gender and age group (n = 517)

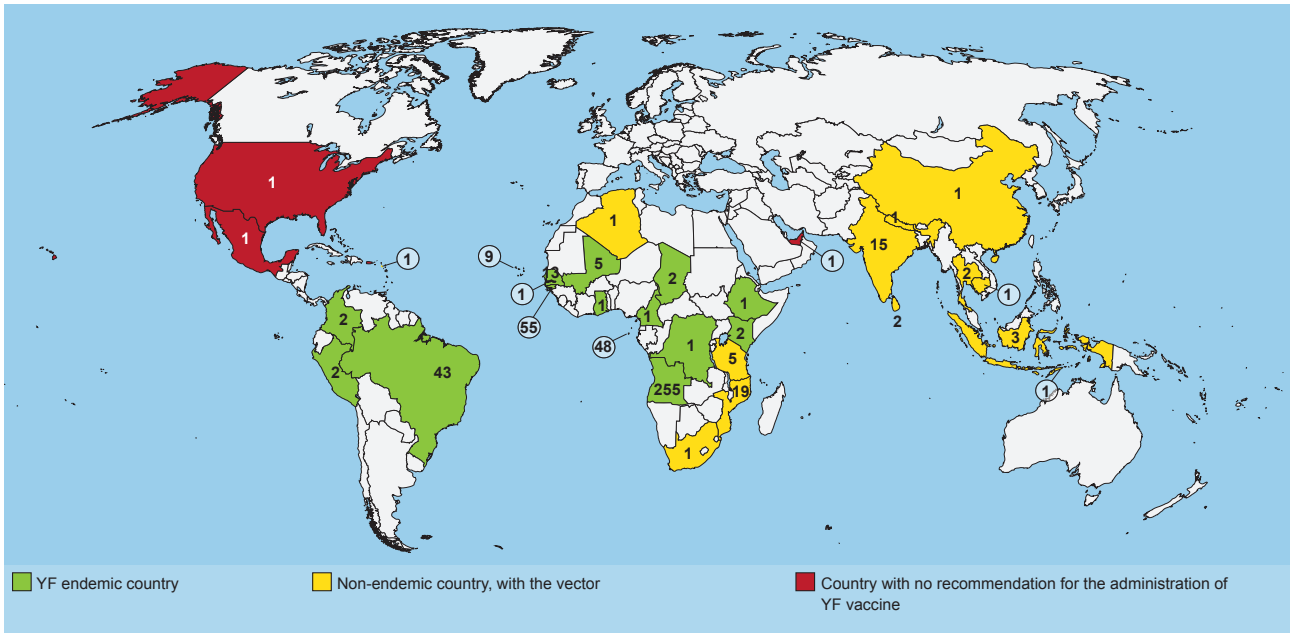

Figure 2 – Number of YF vaccines administered at the no.13 International Vaccination Centre, per country, in 2016 (n = 499)

international studies describing an over-vaccination when the vaccine was mostly prescribed by unexperienced physicians.[14–16]

Even though it is considered as a safe vaccine, its prescription and administration should be individually considered within a risk-benefit balance by healthcare professionals.[20,21] Patients aged 60 and over should have specific indications for the vaccine, due to a higher risk of adverse effects such as neurotropic and viscerotropic disease in case of primary vaccination.[6,9–11] In this study, patients within this age group travelling to an YF non-endemic country were referred by non-specialist consultations. The records did not allow to determine whether these administrations corresponded to a primary vaccination. With the recognition by the WHO of a single dose as conferring life-long immunity, mostly primary vaccinations will become a routine in patients aged 60 and over. The assessment on whether these vaccinations non-compliant with the standard prescription recommendations would be justifiable due to other reasons (for instance, in case that a patient had described a subsequent travel destination and was prescribed with the vaccine in that context at a travel medicine clinic and only the destination of a first travel had been described at the international vaccination centre) or whether this was due to the unawareness regarding the more recent and updated recommendations. The fact that this was a retrospective study using an existing database was another limitation, due to the absence of records, namely personal history, patient contraindications and vaccine-associated adverse effects.

The assessment of prescription adequacy does not allow, on its own, to fully assess the quality of travel health advice; knowledge on other issues apart from vaccination must be provided, including other vector, water and food-borne diseases and road safety, among others.[1] A travel medicine clinic provides a medical approach tailored to each patient and travel destination, including the approach to the prevention of health problems and where ideally the YF vaccine should be prescribed.[20]

Different approaches to an improved quality of travel health advice related to the prescription of YF vaccine can

Table 1 – Outpatient referral for the YF vaccine and patient's travel destination (n = 499)

		Outpatient referral			
		Travel medicine consultation		Non-specialist consultation	
		n	%	n	%
YF endemic country		114	91.2	272	72.7
Non-endemic country with the vector	YFV required when coming from or in transit at a YF country	5	4	59	15.8
	YFV required when coming from or in > 12 h transit at a YF country	5	4	37	9.9
	YFV required when coming from a YF country	1	0.8	3	0.8
No recommendation		0	0	3	0.8
Total		125	100	374	100

YF: yellow fever; YFV: yellow fever vaccine

Table 2 – Outpatient referral and patient's travel destination in patients aged 60 and older (n = 64)

		Outpatient referral			
		Travel medicine consultation		Non-specialist consultation	
		n	%	n	%
YF endemic country		18	100	38	84.4
Non-endemic country with the vector	YFV required when coming from or in transit at a YF country	0	0	5	11.1
	YFV required when coming from or in > 12 h transit at a YF country	0	4	2	4.4
	YFV required when coming from a YF country	1	0	0	0
No recommendation		0	0	0	0
Total		18	100	45	100

YF: yellow fever; YFV: yellow fever vaccine

be found in literature. In New Zealand, the YF vaccine is prescribed by physicians with a postgraduate qualification in travel medicine.[22] In The Netherlands, travellers may select from a list of certified professionals.[23,24] A program for registration, training, standard code of practice and auditing of YF vaccination centres has been developed in the United Kingdom, which has allowed for greater confidence in healthcare professionals when prescribing this vaccine.[13,25,26] In France, a decision-support application has been made available to physicians.[16]

Some of these approaches can be adopted in Portugal in order to ensure the quality of travel health advice, namely involving (i) ongoing training in travel medicine by attending training courses or meetings for knowledge update on YF geography and epidemiology; (ii) certification and auditing of physicians prescribing the YF vaccine; (iii) recognition of the expertise in travel medicine. The international vaccination centres should have a crucial role in monitoring and the assessment of an adequate prescription of the YF vaccine.

Current knowledge on the quality of travel health advice is still scarce, mainly in Portugal. Only the appropriate prescription of the YF vaccine regarding travel destination and the type of outpatient referral has been analysed and the understanding on the relationship between these different prescription profiles and the quality of travel health advice should be improved in further studies.

Therefore, we reached the conclusion that the rate of travellers to YF non-endemic or intermittently epidemic countries was higher in patients referred by non-specialist consultations. All travellers aged 60 and older to a non-endemic country were referred by non-specialist consultations. The vaccine was mostly administered to female patients and to patients aged 40 - 49.

Further studies aimed to fill in the gaps underlying an inadequate prescription of the YF vaccine should be carried out, considering the different reasons for prescription, namely subsequent travel to endemic countries at short-term, female travellers wishing to get pregnant and travellers starting immunosuppressive or immune-modulatory treatments.

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OBSERVATIONS

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HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to regulations established by the Ethics and Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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