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Original article

Acceptance of yellow fever vaccine in the older traveller: a cohort study

Pietro Ferrara[1,2], Cristina Masuet-Aumatell[3,4], Josep Maria Ramon-Torrell[3,4]

[1]Center for Public Health Research, University of Milan, Bicocca, Monza, Italy; [2]Value-based Healthcare Unit, IRCCS MultiMedica, Milan, Italy; [3]Bellvitge Biomedical Research Institute (IDIBELL), Preventive Medicine Department, University Hospital of Bellvitge, Catalonia, Spain; [4]Clinical Science Department, School of Medicine, University of Barcelona, Spain

Abstract. *Background and aim:* Current demographic changes and improvement of quality of life of elderly population have direct consequences on international travelling. The older traveller demands for specific care and precautions to be observed, as for the yellow fever (YF) vaccination, due to the increased incidence rate of adverse events following immunization (AEFI) in people aged 60 years or over. The aim of our study was to determine the adherence to YF vaccine and travel behaviours in a sample of elderly travellers moving to YF endemic areas. *Methods:* Participants in this cohort study were offered YF vaccine, and informed about the increased risk of AEFIs and the unavoidable risk of acquiring YF at the destination. The research was planned on survey-based design, using pre- and post-travel questionnaires. *Results:* In 2018, 239 travellers aged 60 years or older attended our travel clinic, of whom 36.8% (n = 88) planned to travel to YF endemic areas and 23.0% (n = 55) for the first time. Of these, 63.6% accepted and 36.4% rejected the vaccination, with 15 travellers moving to endemic areas without immunization, including one patient who presented contraindications to YF vaccine. *Conclusions:* The presence of more than a third of elderly travellers who travelled without vaccination is a substantial public health problem and, since the number of older travellers continues to increase, it becomes necessary to implement robust actions to improve YF vaccine advocacy and adherence. (www.actabiomedica.it)

Key words: adherence, older traveller, yellow fever vaccine, safety

Introduction

Yellow fever (YF) disease is a mosquito-borne acute haemorrhagic fever caused by a *Flavivirus*, occurring on endemic and intermittently epidemic levels in Africa and tropical South America, and transmitted by different vectors, namely *Aedes* spp., *Haemagogus* spp., and *Sabethes* spp. (1,2). YF shows a severe spectrum of illness, with a case-fatality rate ranging from 20 to 50% (3). Vaccination is recommended for people aged ≥ 9 months who live in or travel to endemic areas. In fact, people travelling to endemic regions represent a population at risk for YF virus exposure, also depending on travellers' and travels' characteristics, such as destination, itinerary, planned activities, travel duration, season, and virus transmission rate in the destination area (4,5).

Two live attenuated vaccines — 17DD and 17D-204 — are available against YF virus, both manufactured from the 17D viral strain (6), being the 17D-204 the licensed vaccine available in Europe. Adverse events following immunization (AEFI) have been reported after YF vaccine inoculation (7-10), subdivided into not life-threatening minor/moderate AEFIs (i.e. local reactions at the injection site, fever, gastrointestinal reactions, etc.) and serious AEFIs. Among the latter, two severe sequelae-causing complications have been described: YF Vaccine-Associated Neurologic Disease

(YEL-AND) and YF Vaccine-Associated Viscerotropic Disease (YEL-AVD). YEL-AND is a conglomerate of neurological syndromes due to infection of the central nervous system with the live attenuated virus from the vaccine. It may include neurotropic diseases (meningoencephalitis, encephalomyelitis, Guillain-Barré syndrome) and autoimmune diseases (such as limb weakness, absent tendon reflexes, cranial nerve abnormalities, altered mental status and ataxia). YEL-AVD mimics the wild-type disease, possibly leading to shock and multi-organ failure (11).

The world's population is not only ageing, but also ageing healthy (12). The number of older persons — those aged 60 years or over — is expected to double by 2050 and to triple by 2100, rising from 962 million globally in 2017 to 2.1 billion in 2050 and 3.1 billion in 2100 (12). Between 1950 and 2050, an astonishing 30 years will have been added to life, therefore more elderly people are expected to move with specific travel-related health risks and needs (12-15).

As regards YF immunisation in elderly, there are data to support an increased risk of AEFIs in people older than 60 years, with the YEL-AND incidence rate of that switches from 0.8 to 2.2 cases per 100,000 doses administered, while the rate of YEL-AVD changes from 0.3 to 1.2 per 100,000 doses (16,17).

Therefore, in travellers aged 60 years or older, YF vaccine should be administrated following a balanced assessment between the risk of vaccine-associated AEFIs and the unavoidable risk of acquiring YF at the destination, also discouraging older travellers at travelling to high-risk endemic areas or changing their travel route, in order to avoid risk exposure (18).

With this study, we aimed at assessing YF vaccination acceptance and travel behaviours in a sample of travellers aged 60 years or older, when informed about the increased risk of YF-vaccine AEFIs.

Materials and methods

Study design

A prospective cohort study was conducted at the Travel Health Clinic at the Hospital Universitari de Bellvitge (Barcelona, Spain) among persons aged 60 years or older who consecutively presented at our clinic in 2018 (January – September) and planned to travel to YF endemic areas. The Institutional Ethics Review Board approved the study protocol and instruments.

Participants

Adults seeking medical advice at the travel clinic, before travelling to YF endemic areas, who agreed to participate in the study and to be contacted after the trip were included. Individuals who met the following criteria were excluded: younger than 60 years old; not willing to participate; or previously vaccinated against YF. This was confirmed through the presentation of the International Certificate of Vaccination or the consultation of the Electronic Medical Records HC3 System (2,19).

The participation was voluntary, participants were not offered any financial incentive and they were informed about their right to withdraw at any time, without penalty. All participants provided written informed consent. Confidentiality was maintained by omitting any personal identifying information from data collection. Phone numbers and email addresses were registered for the follow-up procedures.

Outcomes and instruments

Information were gathered through two questionnaires: the first was completed face-to-face prior to the trip and during the medical visit (*baseline questionnaire*) and the second completed by phone or email from seven days after the expected return date (*post-travel questionnaire*). Both questionnaires were initially tested in a convenience sample of travellers and some items amended for clarity. Additionally, in order to minimize underreporting of important data, the Electronic Medical Records HC3 System (19) was surfed to evaluate the occurrence of possible health events related to vaccination and travel amongst participants.

The questionnaires were based on five areas: demographic (age, gender, country of origin); medical history (comorbidities, pharmacological treatments); travel information (destination, itinerary, duration, and

purpose), YF vaccine hesitancy (measured by acceptance or refusal) and safety (adverse events following immunization).

Risk countries and areas are identified by the 2017 US Center for Disease Control and Prevention (CDC) YF maps (20).

Study procedures

A trained medical doctor systematically provided extended information about efficacy and safety of YF vaccine amongst elderly travellers; accepted questions and concerns about the YF immunization; used decision aids information tools; considered the possibility of re-booking another appointment to further discuss the risk balance with patients, if the time to travel permitted it (19); administered the pre-travel questionnaire. In order to measure the occurrence of the outcomes of interest (vaccination acceptance or refusal, number of vaccine-related adverse effects, and travel related health-problems), an active follow-up data collection was carried out through inviting travellers to contact, by phone or e-mail, or return to our clinic for any symptoms or illness they would experience after the vaccine administration, as well as during and after the travel. All patients are instructed to implement personal preventive measures in order to avoid mosquito bites and prevent YF transmission, independently of their vaccine acceptance or refusal. Subsequently, study participants were contacted from seven days after the expected date of return by the same trained medical doctor.

Statistical analysis

According to data distribution, a Mann-Whitney U test is used to compare continuous variables, which were summarized by median and range. Categorical variables were described as number and percentage, and compared using chi-square (χ^2) or Fisher's exact tests. The statistical analysis was conducted in two stages, following the model-building strategy proposed by Hosmer et al. (22). After determining the variables significantly associated with the outcome of interest at univariate analyses, those with a *p*-value equal or less than .25 were considered for possible introduction an exact logistic regression model for small samples (23). In the model, the following independent variables were considered for inclusion: country of origin (Spain = 1; others = 0), travel destination (Africa = 1; South America = 0); travel purpose (tourism = 1; professional = 2; visiting friends and relatives (VFR) = 3); travel duration (continuous, in days). Multivariate analysis was conducted according to the step-wise method analysis, where significance levels for exclusion and inclusion of variables in the model were *p*-values of .40 and .20, respectively. Results were expressed as odds ratios (OR) with 95% confidence intervals (CIs). All statistical tests were two-tailed and differences were considered to be statistically significant at a *p*-value equal or less than .05 throughout the whole study. Data were analysed using STATA statistical software v. 13.0 (24).

Results

In the study period, 4028 travellers attended the Travel Health Clinic and 239 (5.9%) were older than 60 years. Of these, 36.8% (n = 88) had planned to travel to YF endemic areas and 33 (37.5%) were previously vaccinated against YF. The vaccine-naïve 55 (62.5%) travellers were invited to participate in the study, thus constituting the study population and accessing the standardized care process of pre-travel counselling. A flow-chart of participants can be seen in Figure. 1.

Of the study population, the majority of participants were men (n = 35, 63.6%), with a median age of 65 years (range 61 - 75), being Spanish (n = 46, 83.6%), travelling to Africa (n = 28, 50.9%) for tourism (n = 44, 80.0%) for a median length-of-stay of 16 days (range 4 - 90). The main characteristics of the study population and travel, according to vaccine acceptance or refusal, are listed in Table 1.

A total of 35 subjects (63.6%, 95%CI 50.9-76.3%) gave consent to YF vaccine administration, without statistically significant differences with those who refused it, except for travel duration, which was shorter in the adherent group. The multivariate analysis showed that the likelihood of acceptance was higher in

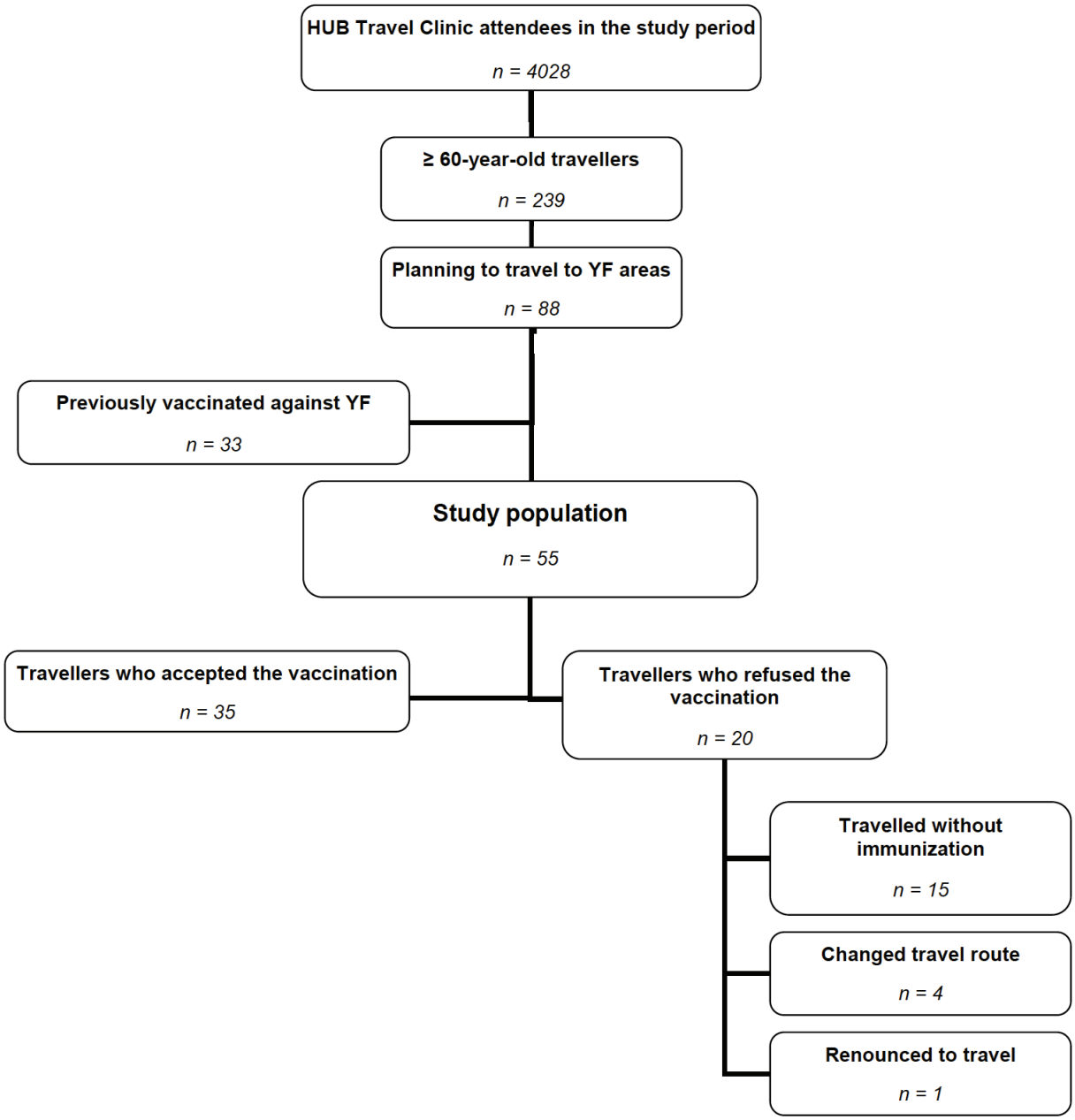

Figure 1. Flow-chart of number of participants in the study.
YF, yellow fever; HUB, Hospital Universitari de Bellvitge

whom travelled to Africa (OR 7.13) and for a shorter period (OR 0.95) (Table 2).

In the non-vaccinated group, four (20.0%) participants decided to change the travel route and one renounced to travel, in order to avoid both the risk of YF disease and vaccine AEFIs. The remaining 15 (75.0%) travellers announced that would travel without vaccination or would not change any travel route. This group included a 72-years-old Senegalese man in immunosuppressive therapy after renal transplantation (tacrolimus and mycophenolate mofetil), who did not

Table 1. Baseline characteristics of study participants (*n = 55*)

	Total	**Travellers who accepted the vaccination (*n = 35*)**	**Travellers who refused the vaccination (*n = 20*)**	***P-value***
	N (%)	*N (%)*	*N (%)*	
Gender (male)	35 (63.6%)	21 (60.0%)	14 (70.0%)	*0.46*
Age° (*in years*)	65 (61-75)	65 (61-75)	64 (61-75)	*0.36*
Country of origin (Spain)	46 (83.6%)	32 (91.4%)	14 (70.0%)	*0.06*
Travel destination				*0.07*
Africa	28 (50.9%)	21 (60.0%)	7 (35.0%)	
South America	27 (49.1%)	14 (40.0%)	13 (65.0%)	
Travel purpose				*0.09*
Tourism	44 (80.0%)	31 (88.6%)	13 (65.0%)	
*Professional**	4 (7.3%)	2 (5.7%)	2 (10.0%)	
VFR	7 (12.7%)	2 (5.7%)	5 (25.0%)	
Travel duration (*in days*)°	16 (4-90)	15 (7-35)	21 (4-90)	*0.01*

° Variable summarized by median and range.
* Also including cooperation purposes.
VFR, Visiting friends and relatives.

Table 2. Univariate and multivariate analyses indicating associations between variables and yellow fever vaccine acceptance.

Univariate analyses			
	OR	***95% CI***	
Gender *Male* *Female*	 1 1.65	 0.48 - 5.02	
Age *(continuous, in years)*	0.93	0.81 - 1.07	
Travel destination *South America* *Africa*	 1 2.79	 0.89 - 8.72	
Travel purpose *Other* *Tourism*	 1 4.17	 1.04 - 16.73	
Travel duration *< 15 days* *≥ 15 days*	 1 0.35	 0.11 - 1.18	
Multivariate exact logistic regression model for small samples			
Model: **Yellow fever vaccine acceptance**			
Model score = 13.78; p = .0004			
Variable	***OR***	***95% CI***	***P-value***
Destination (Africa)	7.13	1.21 - 44.56	*0.03*
Travel duration	0.95	0.90 - 0.99	*0.01*
OR, odds ratio; *95% CI*, 95% confidence intervals			

report previous immunisation and was travelling for VFR to his origin country.

During the follow-up, one traveller (2.9%, 95%CI 0.0-8.4%) contacted our travel clinic complaining fever and arthromyalgias after 12 hours from vaccine administration, which improved with paracetamol 1000mg/bid and resolved, respectively, after 72 hours and seven days.

The consultation of regional medical records found no other adverse events or travel-related problems, both in vaccinated and non-vaccinated groups. No visits to GPs or emergency department were observed.

Discussion

This cohort study provides important data on YF vaccine acceptance and travel behaviours among elderly travellers. Our findings showed that a relevant proportion — more than a third — of older persons refused the YF vaccine when informed about the risk of increased rate of severe AEFIs. Hence, whilst YF vaccine administration in elderly represents a clinical concern, the presence of a third of elderly travelling without vaccination is a substantial public health problem. We did not detect any demographic profile or travel characteristic associated with the adherence to the YF vaccine; however, we acknowledge that our sample size may be underpowered to detect relevant effects and larger studies are needed to investigate underlying behavioural determinants.

In this regard, it should be highlighted that some enrolees refused vaccination even when they were informed about the possibility of a mandatory vaccination for entering certain countries, where incoming travellers that do not present a proof of vaccination certificate are required to undertake YF inoculation (2). In this case, travellers are likely to be exposed to a higher risk compared with the safety that a travel clinic may offer, due to possible less controls in vaccine preservation and administration.

Compliance towards YF vaccination has been analysed in previous research in general or other specific populations, highlighting a variable proportion of travelled not seeking pre-travel medical advice or refusing YF vaccine (25,26). Some drivers have been investigated, with the most important ones being poor risk perception and vaccination hesitancy (25-27), as for other vaccines proposed to travellers (28,29). Indeed, travel-related health risks are variously perceived by travellers, with many of them falsely reassured by the low number of travel-related disease in their home countries (2,28-30).

Other studies also included costs as a possible reason for vaccination refusing or delaying among travellers (31,32). However, the Catalan Healthcare System guarantees low-cost fees and a cost-sharing for this vaccine among travellers.

With regards to YF vaccine, elderly travellers' hesitancy is undoubtedly linked to safety concerns due to higher likelihood of possible adverse effects, even if people that seek medical advices for travel preparation are more likely to trust in the health care professional and system.

Given to the rise in average life expectancy and the creation of conditions for the smooth travelling of older people (decrease in transport fares, accessibility of transports, packaged holidays, increased affordability of travelling itself), a significant proportion of travellers is currently constituted by elderly people, and an expected proportion of persons older than 60 travelling outside their home country is fixed to 12 - 15% by 2025 (33). Within this context, the caring of elderly traveller must be taken as a growing challenge in travel and preventive medicine (2,13-15). They may have health conditions that increase the risk for travel-associated diseases and illnesses (33,34) and which must be considered before and during travel. Major concerns related to the ageing are the coexistence of chronic disease, drug interactions, the physio-pathological modification of human beings, particularly regarding immuno-senescence, resulting in an altered antibody response that may affect the response to vaccines as well as vaccination-related AEFIs, as for the YF vaccine. (13,16).

In interpreting the findings of this study, there are potential limitations that are worth to consider. First, the number of older travellers who visited our clinic was low and likely limited as a real-world study. However, it should be taken into account that ≥ 60-year-old naïve vaccinees constitute a very small proportion

of travellers. Yet, the participants in this study represented the standard travel population, it is possible to state that the selected cohort is representative of the target population. Indeed, similarly to previous studies that investigated infrequent endpoints in travel medicine, the enrolment of a consecutive cohort reduces problems of selection and participant bias (30). Second, even if Catalan regional medical records are constituted by an IT system where patients' medical history is real-time reported, participants may be less likely to seek medical care for minor health problems. These may lead to underestimate the actual incidence of minor adverse events in our cohort, which occurred in 2.9% the participants, while literature describes an incidence between 10% and 30% of the vaccinees (35).

In conclusions, our study provides important findings and describes the behaviours of the elderly people travelling to YF endemic areas, as individuals who share risks exposures and vaccine hesitancies. The population of older travellers continues to increase; therefore, this research highlights the need of designing and implementing prevention measures to improve YF protection in this specific population.

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Correspondence:
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Prof. Josep Maria Ramon-Torrell, MD, PhD
Bellvitge Biomedical Research Institute (IDIBELL),
Preventive Medicine Department,
University Hospital of Bellvitge,
Feixa Llarga s/n, L'Hospitalet de Llobregat, 08907,
Catalonia, Spain.
Email: jmramon@ub.edu.
Phone: +34 93 260 75 57
Fax: +34 93 260 78 49.