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REVIEW

Yellow fever vaccine hesitancy and its relationship with contextual, individual, or group influences and vaccine-specific issues: a scoping review

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Abstract *Vaccine hesitancy is a phenomenon with the potential to reduce vaccination coverage rates, as observed with the yellow fever vaccine (YFV), leading to epidemics and the reintroduction of controlled immunopreventable diseases. This study, together with the scientific literature, aims to map the relationship among the lack of information, vaccine safety and adverse events, and vaccine hesitancy concerning YFV. A scoping review was conducted in the Virtual Health Library (VHL), National Library of Medicine (PubMed), SCOPUS, Embase, and Web of Science databases, using controlled (DeCS/MeSH) and uncontrolled descriptors. In this work, we selected eleven articles, published in English, Spanish, and Portuguese, with no time limits, which met the inclusion criteria. False information, inadequate knowledge about the immunizer, lack of time to take a vaccination, acceptance of the vaccine, vaccine safety, and fear of adverse events were related to vaccine hesitancy. This study reinforces the importance of access to adequate information, provides guidance on YFV safety and adverse events, and can aid in the development of public health strategies to mitigate hesitancy.*

Key words *Yellow fever vaccine, Vaccine hesitancy, Health behavior*

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Introduction

Yellow fever (YF) is an infectious disease caused by a virus from the Flavivirus species and is transmitted to humans by arthropod vectors from the species *Aedes* spp., *Haemagogus* spp., and *Sabethes* spp., from the Culicidae family. It is a disease that is ether endemic or enzootic, found in the tropical forests of Africa and Central and South America, with periodic surges of variable magnitudes[1,2].

A total of 47 countries, 34 from the African continent and 13 from South America, are endemic or have endemic regions for YF[3]. Since the identification and control of the *Aedes aegypti* vector, which is the main factor responsible for urban outbreaks, in 1900, the disease witnessed a significant decline outside of endemic tropical areas[1]. There is no specific viral treatment for the disease, and immunization is the most efficient means through which to control and prevent it, especially in areas where ecological conditions favor the establishment of a transmission cycle[4-6]. High vaccination coverage enables the blocking of transmission by the vector, limiting the risk of infection to the rest of the population[7].

Therefore, as in the case of other vaccines, reaching a broad vaccination coverage for YF is still a challenge for public health. Even though there has been a substantial increase in vaccination coverage against yellow fever since 1970, its heterogeneity, especially in terms of risk areas for the disease, constitutes an important barrier against the control of the disease[8].

Between 1970 and 2016, coverage varied from less than 10% in countries from Central and Eastern Africa (where the routine infant vaccination programs had not yet been introduced) to 100% in the state of Amazonas, Brazil. In Western and Southern Africa, since the implementation of extensive campaigns in 2006, an increase in vaccination coverage has been observed. In Latin America, a low coverage was estimated for Guyana, Suriname, French Guiana, and Colombia. Coverage was particularly high in Brazil (above 90%) during the 1970's and 1980s, with a slight drop in the 1990s, and a heavy upsurge again in 2016[8].

On the other hand, after years of the eradication of the urban cycle, since 2016 (possibly due to flaws in vaccination caused by difficulties in access and vaccine hesitancy), there have been outbreaks of YF throughout Latin America. In Brazil, four of its most populous states have been affected (Minas Gerais, São Paulo, Rio de Janeiro, and Espírito Santo)[9-11].

Considering this scenario, actions involving Vaccine Alliance (GAVI), United Nations Children's Fund (UNICEF), and the World Health Organization (WHO) resulted in the "Eliminate Yellow Fever Epidemics (EYE)" program, which defines, as strategies to expand access to vaccines during emergency epidemics, recommendations for fractional doses and increased surveillance of Post-Vaccination Adverse Events (EAPV, in Portuguese). In Brazil, such a strategy was adopted by some states, as was the recommendation of the YF vaccine (YFV) for the entire territory of Brazil[12-13].

The vaccine produced from the virus strain 17D was developed in 1936 and has been in use since 1937[6]. It has a high immunogenicity (95% to 99% of the people vaccinated develop neutralizing antibodies), and it is considered efficient and safe. Vaccination is recommended for travelers and populations from the areas where the disease is endemic in order to prevent the transference of the yellow fever virus from one country to another[14].

Adverse effects of the vaccine have been reported, with light cases being more common and moderate or severe cases more sporadic[15]. These types of events occur more often due to mass vaccination[16], a situation which is potentially favorable to an increase in the risk perception related to the vaccine[14].

Hesitancy, from the Latin, *hæsitātĭō*, refers to 'indecision, with delay or refusal to take the vaccine', and has specific elements according to context and to the passing of time[11,17]. Studies concerning vaccine hesitancy are scarce in the literature, representing a lack of knowledge that must be addressed, considering that the reintroduction of the disease in urban scenarios is an important public health risk[12]. Some studies have suggested that vaccine hesitancy is influenced by the quality of information or the lack thereof, as well as by an increase in the many reports on adverse effects related to the YFV, which have occurred in recent years, thus causing fear in the very population that should receive the vaccine[13]. Therefore, this study proposes to investigate, in the literature, if the lack of information on adverse effects or regarding the safety of the vaccine are related to vaccine hesitancy against the YFV.

Methodology

This is a scoping revision that seeks to identify and describe articles available in the scientific literature that address the lack of information, adverse events, and vaccine safety in relation to hesitancy against yellow fever vaccine. For this revision, we followed the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR).

Methodological procedure

This study was conducted in six phases: (1) formulation of the research question; (2) identification of relevant studies; (3) selection of the studies; (4) data mapping; (5) collection, summary, and description of the findings; and (6) publication of the results[18].

Beginning with the research question, "Do adverse events and/or lack of information and/or safety of the vaccine contribute to hesitancy against the yellow fever vaccine?", the elements were defined according to mnemonics: P – Population, C – Concept, and C – Context (P (population exposed to vaccination); C (yellow fever vaccine), and C (vaccine hesitancy)). Since it is a contemporary concept, other search terms which are less comprehensive, yet widely mentioned in literature, such as trust and its derivatives, acceptance or vaccine acceptance[17], were also used in the bibliographic search, with the purpose of mapping studies which proposed to investigate vaccine hesitancy.

The definition and characterization of vaccine hesitancy by the Strategic Advisory Group of Experts Working Group on Vaccine Hesitancy (SAGE-WG) were used to divide the results into three categories: contextual influences, individual and group influences, and matters specific to the vaccine or the vaccination[17].

Data sources

The databases selected for the search were: Virtual Health Library (*Biblioteca Virtual em Saúde – BVS*), Scientific Electronic Library Online (SciELO), Latin-American and Caribbean Literature in Health Sciences (LILACS), National Library of Medicine (PubMed), SCOPUS, Embase, and Web of Science. The controlled descriptors (Health Sciences Descriptors (DeCS), Medical Subject Headings (MeSH)], and the uncontrolled descriptors (keywords) were defined in order to ensure a detailed search.

Data collection and organization

The controlled and the uncontrolled descriptors were synthesized according to the population, concept, context (PCC) strategy. The combinations for the construction of strategies are described in Chart 1. The search in the data banks took place on December 10 and 11, 2021. The selection of studies was conducted independently by two different authors, the results were compared and the divergences and doubts were solved by a third author. Moreover, in an attempt to find articles that answered the research question but that were missed during the search in the databases, we also conducted a search in the references of the selected studies.

Publications in English, Spanish, and Portuguese were included, with no time limits, intending to cover the highest number of publications dealing with vaccine coverage, vaccine safety, adverse effects after vaccination, and/or knowledge, considering the hypothesis that vaccine hesitancy is closely related to those dimensions. Moreover, duplicate articles were excluded, as were clinical essays and those concerning fractional vaccine doses against YF, case studies, studies about patients with previous comorbidities, articles about the vaccine's protection against YF, articles about vaccine hesitancy which do not mention YF, and theoretical essays focused on the description of actions to reduce vaccine hesitancy. Articles that did not answer the research question were excluded in later phases (Figure 1).

The articles were mapped using a form for data extraction, created in Microsoft Excel, version 2019, containing: title; author(s); area; country of origin; kind of study; periodical; objective(s) of the study; place of research; period of the study; context; situation of outbreak or not; participants (quantity and characteristics); data collection (instrument for evaluation and finality); criteria of inclusion and exclusion; definition of vaccine hesitancy and the authors; objective achieved or not, main results and others; information about risk factors of the vaccine; and limitations of the study. We also used the definition and characterization of vaccine hesitancy proposed by SAGE-WG to divide the results according to the category[17]. The risk of bias in the studies was not evaluated, since this is a scoping revision, but quality was ensured through a rigorous application of the inclusion and exclusion criteria, considering several quality aspects, as described above.

Chart 1. Databases, search strategy and number of articles selected, Brazil, 2021.

Databases (Total texts)	Search Strategy (Articles found)	Articles found	Articles selected
BVS (LILACS and SCIELO) (4,506)	"Vaccine against yellow fever" AND "Safety" AND "Adverse events" OR "Collateral effects and drug-related adverse reactions	37	0
	"Yellow fever vaccine" AND "Safety" AND "Drug-Related Side Effects and Adverse Reactions"	18	0
	"Yellow fever vaccine" AND "Safety" OR "Patient safety"	1558	2
	"Yellow fever vaccine" AND "Safety" OR "Patient safety"	2695	1
	"Yellow fever vaccine" AND "Vaccination refusal"	2	0
	"Yellow fever vaccine" AND "Vaccination refusal"	2	0
	"Yellow fever vaccine" AND "Patient Acceptance of Health care"	5	0
	"Yellow fever vaccine" AND "Patient Acceptance of Health care"	11	0
	"Yellow fever vaccine" AND "Vaccination coverage"	28	0
	"Yellow fever vaccine" AND "Vaccination coverage"	150	1
PubMed (559)	"Yellow fever vaccine" AND "Safety" AND "Drug-Related Side Effects and Adverse Reactions"	13	0
	"Yellow fever vaccine" AND "Safety" OR "Patient safety" AND "Vaccination refusal"	111	0
	"Yellow fever vaccine" AND "Safety" OR "Vaccine safety" AND "Vaccination refusal"	300	0
	"Yellow fever vaccine" AND "Safety" OR "Vaccine safety"	2	0
	"Yellow Fever Vaccine" AND "Vaccination refusal"	1	0
	"Yellow Fever Vaccine" AND "Patient Acceptance of Health care"	19	1
	"Yellow Fever Vaccine" AND "Vaccination coverage"	113	0
Scopus (2,116)	"Yellow fever vaccine" AND "Safety" AND "Adverse events" OR "Drug-Related Side Effects and Adverse Reactions"	1	0
	"Yellow fever vaccine" AND "Safety" AND "Drug-Related Side Effects and Adverse Reactions"	85	0
	"Yellow fever vaccine" AND "Safety" OR "Patient safety" AND "Vaccination refusal"	62	0
	"Yellow fever vaccine" AND "Safety" OR "Vaccine safety"	3	0
	"Yellow fever vaccine" AND "Safety" OR "Vaccine safety"	697	0
	"Yellow fever vaccine" AND "Vaccination refusal"	1	0
	"Yellow fever vaccine" AND "Vaccination refusal"	87	0
	"Yellow fever vaccine" AND "Patient Acceptance of Health care"	133	3
	"Yellow fever vaccine" AND "Vaccination coverage"	3	0
	"Yellow fever vaccine" AND "Vaccination coverage"	1044	0
Embase (785)	"Vaccine against yellow fever" AND "Safety" AND "Adverse events" OR "Collateral effects and drug-related adverse reactions	1	0
	"Yellow fever vaccine" AND "Safety" AND "Drug-Related Side Effects and Adverse Reactions"	2	0
	"Yellow fever vaccine" AND "Safety" OR "Patient safety" AND "Vaccination refusal"	3	0
	"Yellow fever vaccine" AND "Safety" OR "Patient safety"	697	0
	"Yellow fever vaccine" AND "Vaccination refusal"	4	0
	"Yellow fever vaccine" AND "Vaccination coverage"	78	1
Web of Science (847)	"Yellow fever vaccine" AND "Safety" AND "Drug-Related Side Effects and Adverse Reactions"	2	0
	"Yellow fever vaccine" AND "Safety" OR "Patient safety" AND "Vaccination refusal"	534	0
	"Yellow fever vaccine" AND "Safety OR Patient safety"	217	0
	"Yellow fever vaccine" AND "Vaccination refusal"	3	0
	"Yellow fever vaccine" AND "Vaccination coverage"	91	0
Total		8,813	9

Source: Authors.

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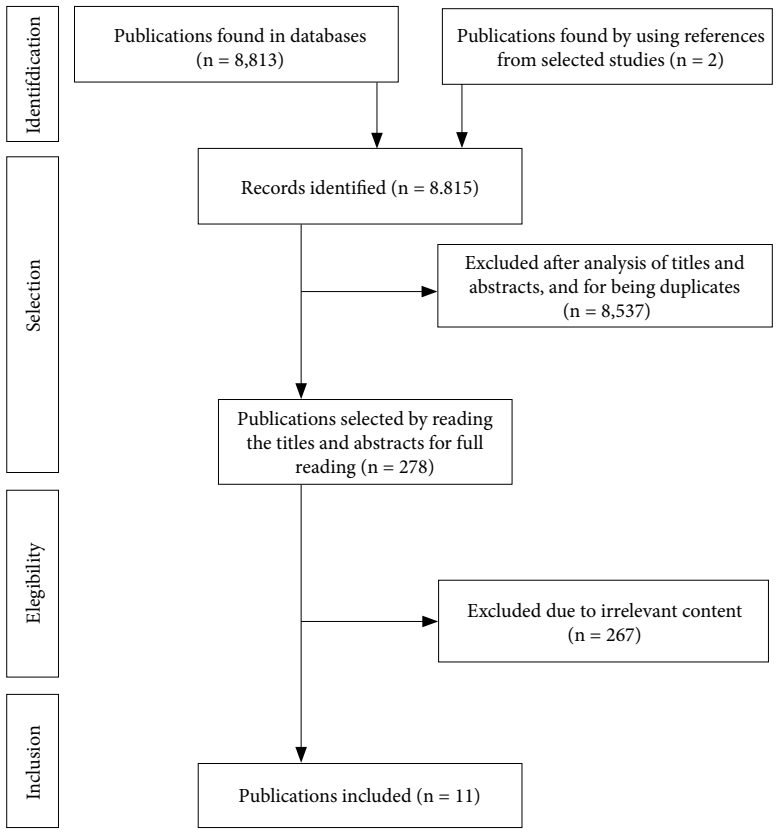

Figure 1. Flowchart of the search and sorting of the articles for the scoping revision, Brazil, 2021.

Source: Authors.

Data analysis

The results were described by figures in which the key information from the studies was synthesized, and were interpreted and compared in order to describe the evidence which responds to the research question.

Ethical aspects

Since this study is a scoping revision, the reliability and trustworthiness of the information from the selected publications was guaranteed, through referencing and care with the data and its presentation.

Results

Eleven publications were included: nine were found in the databases and two more were recovered upon verifying the bibliographic references of the selected articles. Nine publications (81.8%) consisted of cross-sectional studies, one (9.1%) was a cohort study, and the last was a qualitative exploratory study (9.1%). These were retrieved from ten different countries, predominantly from the American continent (n = 4) (Brazil, Peru, the United States of America); three were European studies, from Turkey (Eurasian), and France; and three were from African countries (Angola, Nigeria, and South Africa). In seven of the 11 studies (63.6%), the population sample was made up of travelers or people preparing to travel. The characteristics referring to the studies, such as title, study design, country of origin, and year of publication are described in Chart 2.

Chart 2. Characteristics of the 11 studies that composed the sample for our scoping review, according to title of the article, study design, country of origin, and year of publication, Brazil, 2021.

Title	Kind of study	Country	Year of publication
Notes from the field: knowledge, attitudes, and practices regarding yellow fever vaccination among men during an outbreak – Luanda, Angola, 2016[29]	Cross-sectional	Angola	2017
Fake news sobre vacinas: uma análise sob o modelo dos 3Cs da Organização Mundial da Saúde[33]	Qualitative exploratory	Brazil	2021
Travel health attitudes among Turkish business travellers to African countries[22]	Cross-sectional	Turkey	2016
Vaccination knowledge, attitude and practice among Chinese travelers who visit travel clinics in Preparation for international travel[23]	Cross-sectional	China	2016
Evaluación de cobertura y del nivel de información en la campaña de vacunación contra la fiebre amarilla, Cusco, Perú, 2005[30]	Prospective, Descriptive Cross-sectional	Peru	2008
Acceptance of yellow fever vaccine in the older travelers: a cohort study[28]	Cohort	Spain	2021
Preferences and decision needs of Boston-area travelers to countries with risk of yellow fever virus transmission: implications for healthcare providers[24]	Descriptive Cross-sectional	USA	2014
Vaccination against yellow fever in French Guiana: The impact of educational level, negative beliefs and attitude towards vaccination[31]	Descriptive Cross-sectional, population based	French Guianna (France)	2017
Knowledge, attitude and compliance towards travel vaccines among Nigerian travelers at an international airport[25]	Descriptive Cross-sectional	Nigeria	2019
Travelers' knowledge, attitudes and practices on the prevention of infectious diseases: results from a study at Johannesburg International Airport[26]	Cross-sectional	South Africa	2004
Travel health knowledge, attitudes and practices among United States travelers[27]	Cross-sectional	USA	2004

Source: Authors.

The contextual information mentioned in the selected studies refer to knowledge and beliefs (religious; concerning the need for vaccination; vaccine efficiency), followed by level of education and attitudes (negative/recommendation) in relation to the vaccine. The individual and group influences most commonly mentioned were the fear related to vaccine safety, to adverse effects, or to age. In the category of issues specifically related to the vaccine, cost was mentioned in relation to vaccine hesitancy (Figure 2).

Discussion

Most of the analyzed studies are from endemic areas of YF or from areas with a potential for severe urban outbreaks of the disease, such as the case in some regions of China and USA[19]. Most of the studies are cross-sectional, conducted with people traveling or preparing to travel. We observed that the expression "vaccine hesitancy" is still incipient, mainly in relation to the YFV. However, "trust" and its derivatives, "acceptance" or "vaccine acceptance"[17], "vaccine delay" and "vaccine refusal" are more common and more commonly studied[17,20,21].

The vaccine hesitancy phenomenon is influenced directly by the particular characteristics of each population, such as the socioeconomic, cultural, and immunobiological contexts[17]. Two kinds of studies were identified: the first, produced in developed countries free of the diseases of interest or with populations from developed countries free of the mentioned diseases. These refer to travelers who visit countries that are endemic for infectious immune preventive diseases. In those studies, the main factors are related to risk perception regarding the disease, to vaccine acceptance, and to vaccine costs. Other

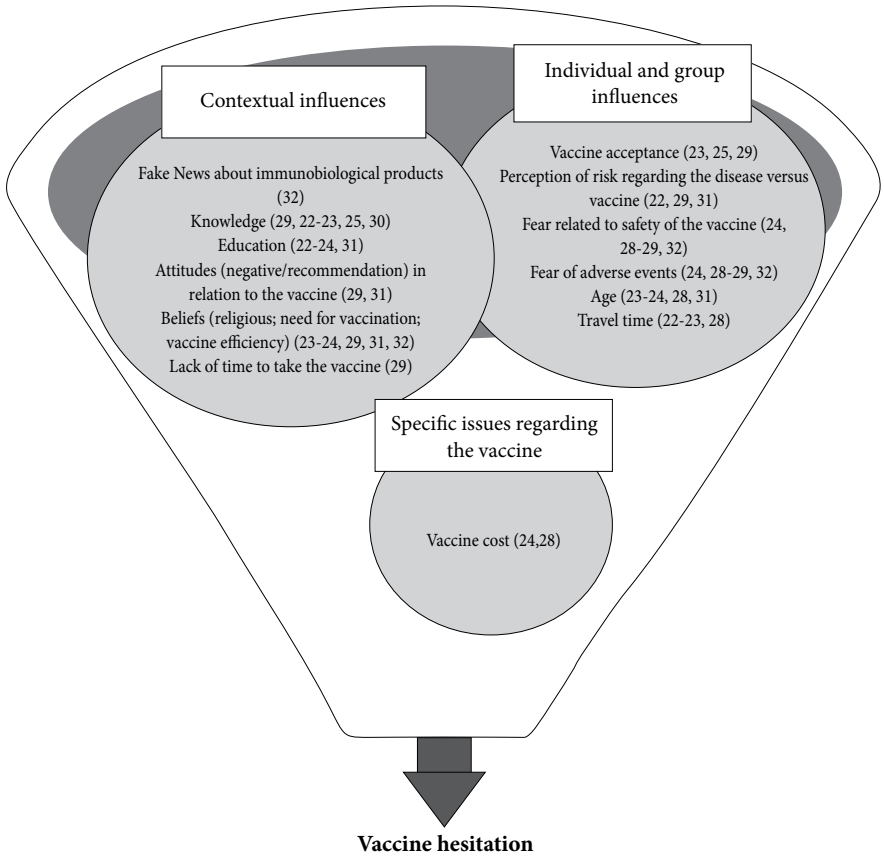

Figure 2. Factors associated with vaccine hesitancy mapped in the studies according to categories defined by SAGE-WG17, Brazil, 2022.

Source: Authors.

factors refer to the individuals' knowledge about the disease, as well as the need to take vaccines and to acquire travel advice from specialized services[22-27] or from centers that evaluate the attitudes and vaccine acceptance among travelers who are informed about the risks of adverse effects of the YFV[28]. In those cases, there is a prevalence of concerns regarding the risks of the trips, the exposure of travelers to the disease, and the risk of importing the disease to the countries of origin.

The second pattern found in the studies refers to the countries that are endemic to the diseases as well as to developing countries with established immunization programs, in which there is a concern about the factors that interfere directly on the low rates of vaccine coverage, effectiveness of the vaccine awareness campaigns, and knowledge about the vaccine and the disease[29-31]. In these studies, the main goal seems to be related to the advice concerning the necessary measures to deal with possible outbreaks or re-emergence of the disease. In this group, there are more specific studies about the factors related to hesitancy against the YFV.

Our study found a predominance of factors associated with the "Contextual Influences" category, especially the issue of evaluating the knowledge and attitudes concerning immunobiological agents, connected to risk perception regarding infectious immunopreventable diseases, especially among travelers[22-23,25,27-28]. An interconnection was found among the factors related to vaccine hesitancy within this category, ranging from poor access to information, which may be incomplete or fake, to the construction of an

inadequate knowledge, which reverberates in the introjection of beliefs, attitudes, time priorities, and inadequate decision-making regarding the vaccine[17,21,31,32].

The studies which analyzed knowledge and attitudes in relation to immunobiological agents and studies which looked into those factors especially for the YFV, reported unsatisfactory to poor levels of vaccination or to negative attitudes which heavily influence the increase in vaccine hesitancy[22,25,29-30]. Nevertheless, they did find a positive relationship between having a higher level of education and access to information by means of the visas for the destination countries, advice provided by the travel agencies and by friends and family, with YFV acceptance rates reaching nearly 99.8% for those who were informed that the destination country required a vaccination[23]; as well as the higher level of education of the parents related to the higher vaccine coverage of their children[31].

Our study identified that the availability of information and the easy access to it, combined with favorable socioeconomic conditions, were not always related to satisfactory knowledge for the acceptance and expression of positive attitudes or to adequate risk perception regarding the vaccine[26-27].

Widely spread information that is proven to be false has the potential of leading to error, resorting to sensationalism, social panic, and an accusatory tone to help its dissemination[32,33], which is heavily related to a decline in vaccine coverage around the world[33], since most of that false information is aimed at vaccines. Alice Frugoli *et al.*[32] reported that 55% of the fake information available in three sites analyzed in Brazil in 2018 referred to biological agents, and 63% to the YFV, spreading information which primarily questioned the safety and effectiveness of the immunization. Brazil is one of the countries that suffers the most with the influence of false information affecting vaccine coverage[34].

Akoï Koïvogui *et al.*[31] reported that participants without negative beliefs had a 30% higher chance of taking the vaccine, as compared to those with negative attitudes, who were 40% less likely to take the vaccine. These same participants mentioned religious or cultural motives and indifference towards the vaccine as reasons for not being vaccinated.

The working hours of the health services[29] and difficulties in accessing the vaccination facilities[29,31], either due to a lack of knowledge regarding the location or distance to those facilities, were also reported as important contextual factors for vaccine hesitancy. The distance between the subjects' home and the vaccination facilities was related to a 40% lower chance of vaccination[31]. Studies in which people reported time clashes between their working hours and vaccination hours also mentioned negative attitudes, such as unwillingness to wait in line for the vaccine and the perception that the YFV is dangerous[29,31], which leads to the hypothesis that the lack of time is not the real reason for those individuals' refusal to take the vaccine.

Concerning the individual and group influences, vaccine acceptance is influenced by several factors, including the mandatory requirement for vaccination by the countries of destination[23,25], being female[23,35], having countries from South America and Africa[28] as a destination, and the duration of the trip. The rate of vaccine acceptance was higher among the travelers who were spending a short time in the country; duration of the visit and the acceptance of the immunization were inversely proportional[22-23,28].

Travelers, aged 50 years and over, showed a higher refusal rate in comparison to younger travelers, which relates to the security concerns, since there is a higher probability of occurrence of adverse effects related to the vaccine in that age group[24]. The lack of concern regarding the disease is a strong reason for vaccine hesitancy in terms of other immunizing agents, as in the case of influenza, for instance[36]. By contrast, Min Zhang *et al.*[23] observed that acceptance was higher as age increased; that relation was also observed in another study which focused on the influenza vaccine[36].

Also associated with non-acceptance of the vaccine is the fear regarding the vaccine's safety and the fear of having severe adverse events associated with the YFV, such as hypersensitivity reactions - especially anaphylaxis and urticaria, which are more prevalent among those who are allergic to eggs or to other components of the vaccine. Other conditions associated with non-acceptance include neurotropic diseases associated with the vaccine, the Guillain-Barré Syndrome; acute encephalomyelitis; and viscerotropic diseases related to the vaccine[3,14].

The perception of the risk in terms of "disease versus vaccine" has been widely discussed in recent years, especially in terms of the re-emergence and reintroduction of immunopreventable diseases, which is based on the idea that those diseases are no longer a risk for the population - that belief is directly based on the decline and eradication of those diseases[17,21-22,31,32]. The studies

found in the literature describe that people do not believe that they are at risk[22] and that the disease is not really important.

Concerning specific matters related to the vaccine, the cost of immunization was the only issue mentioned in the mapped studies[24,28], and that issue differed in the decision-making process of taking the vaccine or not. It is important to note that the health systems in the countries analyzed in this study are quite distinct from each other, which was considered in studies based on populations from countries that do not have consolidated immunization programs, such as Turkey and French Guiana, and which are not justifiable in countries where the YFV is made available for free through immunization programs, as in Brazil, Peru, and some African countries, for example.

The limitations in this study refer to the difficulty in mapping studies which dealt with the term "vaccine hesitancy" in its integrality and coverage, combined with the fact that many of the studies dealt with a set of immunizing agents, in which the YFV was included.

In this review, we were able to illustrate that, in the category of contextual influences, the factors that contribute the most to YFV hesitancy were false information related to immunobiological agents[33]; inadequate knowledge[22-23,25,29,30]; negative attitudes and attitudes of not-recommending the vacccine[29,31]; beliefs, be they religious, or referent to the need for vaccination or the vaccine's efficience[23,24,29,31,32]; lack of time for vaccination[29]; and difficulty in access to vaccination hubs[30]. In terms of individual and group influences, the prevailing factors included vaccine acceptance[23,25,29], risk perception in terms of disease versus vaccine[22,28,31], concerns regarding vaccine safety[24,28-29,32], concerns regarding adverse events[24,28-29,32], age[23-24,28,31], and time to be spent in the country in the case of travelers[22-23,28]. In the specific question category, the cost of the immunization is an important factor influencing vaccine hesitancy[24,28].

This study contributes to the knowledge of the factors related to hesitancy against the YFV, and its use may offer support for the elaboration of public health strategies aimed at reducing vaccine hesitancy, allowing for an increase in YFV coverage, thereby avoiding the increase in cases of the disease.

Collaborations

VS Lopes, PC Souza, JC Lima, and EM Garcia were responsible for the conception of this study, and the search and selection of the documents. VS Lopes and PC Souza conducted the data extraction and drafted the final version of the article. All of the authors participated in the critical revision and final approval of the article for publication.

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