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Systematic Reviews

Systematic Reviews

Yellow fever vaccine safety in immunocompromised individuals: a systematic review and meta-analysis

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Abstract

Background: Yellow fever (YF) is an arbovirus with variable severity, including severe forms with high mortality. The vaccination is the most effective measure to protect against the disease. Non-serious and serious adverse events have been described in immunocompromised individuals, but previous studies have failed to demonstrate this association. This systematic review assessed the risk of adverse events after YF vaccination in immunocompromised individuals compared with its use in non-immunocompromised individuals.

Methods: A search was conducted in the MEDLINE, LILACS, EMBASE, SCOPUS, DARE, Toxiline, Web of Science and grey literature databases for publications until February 2021. Randomized and quasi-randomized clinical trials and observational studies that included immunocompromised participants (individuals with HIV infection, organ transplants, with cancer, who used immunosuppressive drugs for rheumatologic diseases and those on immunosuppressive therapy for other diseases) were selected. The methodological quality of observational or non-randomized studies was assessed by the ROBINS-I tool. Two meta-analyses were performed, proportion and risk factor analyses, to identify the summary measure of relative risk (RR) in the studies that had variables suitable for combination.

Results: Twenty-five studies were included, most with risk of bias classified as critical. Thirteen studies had enough data to carry out the proposed meta-analyses. Seven studies without a comparator group had their results aggregated in the proportion meta-analysis, identifying an 8.5% [95% confidence interval (CI) 0.07–21.8] risk of immunocompromised individuals presenting adverse events after vaccination. Six cohort studies were combined, with an RR of 1.00 (95% CI 0.78–1.29). Subgroup analysis was performed according to the aetiology of immunosuppression and was also unable to identify an increased risk of adverse events following vaccination.

Conclusions: It is not possible to affirm that immunocompromised individuals, regardless of aetiology, have a higher risk of adverse events after receiving the YF vaccine.

Key words: immunocompromised, systematic review, adverse events, yellow fever vaccine, Yellow fever

Introduction

Yellow fever (YF) is a viral, febrile, non-contagious infectious disease of short duration and variable severity that remains endemic in the tropical forests of America and Africa, periodically causing isolated outbreaks or epidemics with greater or lesser impacts on public health.[1,2]

YF is caused by an arbovirus belonging to the *Flavivirus* genus and is transmitted by mosquitoes of *Aedes* and *Haemogogogus* species.[1] There is no specific medication for YF, and the treatment is symptomatic. The lethality is between 5% and 10%, a high percentage when compared with other viruses. The most effective measure to control and protect against YF is vaccination.[1]

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In recent years, major epidemics of urban YF have occurred in Angola and the Democratic Republic of Congo (2015/16) and epidemics of wild YF have occurred in Brazil (2017). In more recent years (2018–19), other outbreaks have been reported in Venezuela, Nigeria, Suriname, French Guiana, Mali, Ethiopia, Togo, Gabon, Liberia and Uganda. The YF epidemics that have occurred since 2016 are considered by the World Health Organization (WHO) to be warnings of larger outbreaks and a spread to countries such as India and China, which are home to *Aedes* mosquitoes and 2 billion people who lack immunity against YF.[3,4]

The YF vaccine has been produced from the attenuated 17D viral strain since 1937. Highly immunogenic, it confers immunity to 95–99% of those who are vaccinated. It is indicated for the prevention of YF in people over 9 months of age living in endemic areas or who will travel to these areas.[4] Specific contraindications for the application of the YF vaccine are described, mainly related to individuals with immunosuppression. As it is a live attenuated virus vaccine, caution is recommended in its indication for these individuals, and its administration should be evaluated individually in the presence of outbreaks.[5]

Although recognized as one of the safest vaccines, serious post-vaccination adverse events and even fatal events have been reported and are related to the vaccine's virus ability to replicate in the vaccinated individual.[6] The most common post-vaccinal adverse event are local reactions, such as pain at the application site, and general manifestations, such as fever, headache and myalgia.[7] Serious adverse events associated with YF vaccination include hypersensitivity reactions, acute neurological disease and acute viscerotropic disease associated with the YF vaccine and death.[7,8]

Immunocompromised individuals are distinguished from the general population by their inability to respond to numerous antigenic or infectious stimuli, which makes them more susceptible to developing infectious diseases. Immunization is important to protect these individuals from infections and reduce the risk of serious complications and death.[4]

There are theoretical contraindications to the use of the YF vaccine in immunocompromised individuals, but the increased risk of adverse events has not been confirmed.[9,10,11] Previous systematic reviews have not been able to conclusively determine the relationship between the YF vaccine and adverse events in immunocompromised patients.[12–15] The bibliographic search in these reviews was carried out before 2018, the year of the beginning of the epidemic in Brazil. Furthermore, two reviews did not include data from the grey literature.[12,14] The review by Barte *et al.* (2014)[13] had its population limited to individuals with HIV and restricted the study designs included to randomized clinical trials and cohort studies, and the one by Croce *et al.* (2017)[15] did not include patients with HIV, restricting them to if to other causes of immunosuppression.

Thus, in order to fill this gap, we decided to conduct this study. Depending on an individual's risk of becoming ill due to natural infection and considering the degree of immunosuppression, vaccination may be recommended after a careful and individualized analysis.

The aim of this systematic review was to assess the risk of adverse events after YF vaccination in individuals with secondary immunosuppression due to HIV infection, organ transplants, cancer, who use immunosuppressive drugs for rheumatologic diseases and other diseases when compared with individuals without immunosuppression. This review also intended to assess whether the status of immunosuppression was a risk factor for adverse events.

Methods

The systematic review was performed seeking to meet the requirements of the Cochrane Handbook for Systematic Reviews of Interventions version 6.2.[16] Its report followed the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist[17] and the specific PRISMA checklist for the assessment of adverse events.[18]

The systematic review protocol followed the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA–P) tool[19] and was registered on the PROSPERO platform (CRD42020158807).[20]

The study was guided by two research questions: 'What is the frequency of adverse events in immunocompromised patients due to the yellow fever vaccine?' and 'What is the risk of adverse events in immunocompromised individuals due to the yellow fever vaccine, when compared with nonimmunocompromised individuals?'

Search strategies

The bibliographic search was carried out in the following bibliographic databases: EMBASE, MEDLINE (via PubMed), LILACS, SCOPUS, the Web of Science, Toxiline and the Database of Abstracts of Review of Effects and grey literature databases (Grey, OpenGrey and the CDC Morbidity and Mortality Weekly Report).

A comprehensive search strategy was used, combining descriptors and free terms related to the review question, and adapted to each bibliographic database. The construction of the search strategies was carried out with the help of a librarianship professional (Appendix 1). The search was performed without filters for language and date, including studies published until February 2021.

The bibliographic reference lists of the identified systematic reviews and included studies were searched to detect possible losses in the performed searches.

Study selection and data extraction

The search results were exported to the EndNote® version X reference manager to exclude duplicate references. The selection of studies was performed in two phases (title and abstract analysis and full text analysis). Like in the data extraction phase, the selection procedures were carried out by two independent reviewers (A.J.L.A. and L.W.A.L.), with differences resolved by consensus or, if necessary, by a third independent reviewer.

A 'pilot' phase was carried out with 10% of the publications to ensure that both reviewers used the same inclusion and exclusion criteria. A flowchart was built according to PRISMA standard.

Studies were included in which the population consisted of individuals with secondary immunosuppression (HIV infection,

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undergoing organ transplants, with cancer, using immunosuppressive drugs for rheumatologic diseases and using immunosuppressive therapy for other diseases), regardless of sex and age, who received the YF vaccine and assessed adverse events after the vaccination.

Adverse events of any nature, including local reactions (pain, redness, swelling and itching) and systemic adverse events (arthralgia, fever, headache, malaise, fatigue, myalgia, diarrhoea, nausea/vomiting, abdominal pain, cutaneous rash, dizziness, tremor, bleeding, bruises) and regardless of their severity, were included. Serious post-vaccination adverse events have been defined as those requiring hospitalization and/or persistent disability and death. Non-serious post-vaccination adverse events are any other event that is not included in the criteria for serious post-vaccination adverse events.[21]

Randomized and quasi-randomized clinical trials and observational studies (case reports, case series, cohort design, case–control and cross-sectional) published in Portuguese, English, Spanish and French were included. Both prospective and retrospective studies were accepted.

Letters, editorials, book chapters, news, comments and expert opinions as well as studies with multiple publications (the most current publication was included) were excluded. Studies without the full text available were excluded when three attempts to contact the authors were unsuccessful.

A standardized electronic form for data extraction was created in Epidata® version 3.1. This form was previously tested in 10% of the publications to verify the necessary adjustments and had an instructional document for completion. In case of missing data, we sought to contact the authors with correspondence by e-mail for up to three attempts. In cases where contact was not possible, the study was excluded.

Assessment of risk of bias and the quality of evidence

The assessment of the methodological quality and risk of bias of each study was independently performed using the criteria of the Risk of Bias in Nonrandomized Studies of Interventions tool (ROBINS-I)[22] by two reviewers (A.J.L.A. and L.W.A.L.), with disagreements resolved by consensus or with the assistance of a third reviewer when necessary.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to assess the quality of evidence in the review using the GRADEpro® tool.[23]

Data analysis

The data extracted from the studies were analysed, and the results are presented in tables. A meta-analysis was conducted to generate synthesis measures if the heterogeneity between the results of the studies allowed their combination.

Heterogeneity was measured by the chi-square test (Chi^2) and the Higgins inconsistency test (I^2) with an assumed significance level of $P < 0.05$. In cases of low or moderate heterogeneity (<70%),[24] the results were combined, and a meta-analysis was performed using the *meta* and *metafor* R® software package.

Two types of meta-analyses were performed. In the studies without a comparator group, a proportion meta-analysis was performed to obtain a summary measure of the frequency of adverse events in immunocompromised individuals due to the YF vaccine and its respective 95% confidence interval (CI). The comparison group studies were included in the risk factor meta-analysis.

The choice of fixed or random effects models to generate summary measures was based on statistical heterogeneity.[19] The immunosuppression types and the methodological quality of the studies were used to carry out subgroup analyses, seeking to identify their effects on the results. Publication bias was assessed by funnel plots, Egger's test and Begg's test.[19]

Results

The search identified 845 records in the bibliographic databases and five in the grey literature, totalling 850 records. Additionally, the bibliographic reference lists of literature reviews were searched, with another 32 references being included, with 585 records remaining after the removal of duplicate records. Of the 58 studies evaluated by full text, 25 were included in the systematic review,[25–49] with 13 included in the meta-analysis. The complete flowchart is presented in Supplementary Figure S1.

Characteristics of the studies, participants and interventions

The included studies were published between 2000 and 2020, eight of which were published after 2015, the year the YF epidemic began in Africa (Table 1). A total of 36% of the studies had cross-sectional designs. Most of the studies were conducted in Brazil (28%) and France (24%), with only one being carried out on the African continent.[43]

A total of 1108 participants (737 immunocompromised participants, 225 non-immunocompromised participants and 146 participants lost after recruitment) were included. The participants' ages varied from 5 to 79 years. The main underlying immunosuppressive diseases were HIV infection ($n = 314$) and rheumatoid arthritis ($n = 161$).

The most used immunosuppressive drugs were methotrexate (six studies) and corticoids (four studies). Only 15 studies described the vaccination status (primary or booster) that was used, but without providing individualized data, making it impossible to establish a relationship with adverse events. The 17D lineage of the YF vaccine was the most used (50%), and the unfractionated dose was used in only three studies.

The YF vaccine was used for prevention prior to a trip in 56% of the studies. Most studies (84%) did not report the coadministration of vaccines (Supplementary Table S1).

Risk of bias assessment

All the evaluated studies were non-randomized, and the ROBINS-I tool was used to assess the risk of individual bias (Supplementary Figure S2). No study presented an overall low risk of bias for the evaluated domains. Fifteen studies (60%) had a critical risk of bias, five (20%) had a severe risk of bias and another five had a moderate risk of bias (20%).

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Table 1. Characteristics of the studies included in the systematic review and evaluated participants

Author, year	Study design	Place of conduction	Total sample size (*n*)	Disease (*n*)	Age (years)	Sex (*n*)	Therapeutic scheme (*n*/dose)
Avelino, 2016[25]	Prospective cohort	Brazil	63[a]	HIV (12)	Immunodepressed: 30–47 (Median = 33) Comparison: 31–62 (Median = 43)	Imunodepressed F = 0; M = 12 Comparison F = 23; M = 22	Unspecified antiretroviral (11/ND)
Azevedo, 2011[26]	Cross-sectional	Brazil	19	Kidney transplant (14) Heart transplant (3) Liver transplant (2)	11–69 (Mean = 45.6)	F = 06; M = 13	Azathioprine (7/50–125 mg/day) Cyclosporine (8/100–300 mg/day) Deflazacort (1/12 mg/day) Mycophenolate (10/1000–2000 mg/day) Prednisone (11/5–15 mg/day) Sirolimus (3/2–3 mg/day) Tracholimus (4/2–5 mg/day)
Barwick, 2004[27]	Case series	USA	4	Timoma (4)	44–70	F = 01; M = 03	ND
Bühler, 2020[28]	Prospective cohort	Switzerland	32[b]	Rheumatoid arthritis (4) Psoriatic arthritis (3) Juvenile Arthritis (1) Sarcoidosis (1) Psoriasis (3) Atopic dermatitis (1) Neurodermatosis (1) Ulcerative colitis (1)	Immunodepressed: 31–55 (Median = 53) Comparison: 32–59 (Median = 52)	Immunodepressed F = 09; M = 06 Comparison F = 10; M = 05	Prednisone (1/2.5 mg/day) Metrotexate (15/median 12.5 mg/week)
Ekenberg, 2016[29]	Case report	Denmark	1	Crohn's disease (1)	56	F = 01	Infliximab (1/ND) Metrotexate (1/ND)
Fontbrune, 2017[30]	Cross-sectional	France	21	Bone marrow transplant (21)	5.1–61 (Median = 15.1)	ND	Prednisone (1/2 mg/day)
Gowda, 2004[31]	Case report	UK	1	Bone marrow transplant (1)	50	M = 01	ND
Ho, 2008[32]	Cross-sectional	Brazil	144[c]	HIV (7)	ND	ND	ND
Jong, 2019[33]	Case series	USA	2	Sjögren's syndrome (1) Liver transplant (1)	25–35	F = 01; M = 01	Tacrolimus (1/5 mg/day) Corticosteroid (1/ND) Mycophenolic acid (1/3 g/day)
Kengsakul, 2002[34]	Case report	Thailand	1	HIV	53	M = 01	ND
Kerneis, 2013[35]	Prospective cohort	France	102	Rheumatoid arthritis (9) Chronic inflammatory disease (14) Upper respiratory tract diseases (8) Others not defined (3)	Immunodepressed: 43–59 (Median = 55) Comparison: 46–61 (Median = 55)	Imunodepressed F = 22; M = 12 Comparison F = 39; M = 29	Prednisone (34/Median: 7 mg/day)
Martin, 2001[36]	Case series	USA	4[d]	Crohn's disease (1) Polymyalgia rheumatica (1) Thymoma (1)	67–79	F = 02; M = 01	ND
Miranda, 2020[37]	Cross-sectional	Brazil	6	Kidney transplant (6)	35–66 (Mean = 50)	F = 03; M = 03	ND

(*Continued*)

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Table 1. Continued

Author, year	Study design	Place of conduction	Total sample size (*n*)	Disease (*n*)	Age (years)	Sex (*n*)	Therapeutic scheme (*n*/dose)
Mota, 2009[38]	Cross-sectional	Brazil	70	Rheumatoid arthritis (52) Systemic lupus erythematosus (9) Spondyloarthropathy (5) Systemic sclerosis (2), Systemic lupus erythematosus and rheumatoid arthritis (2)	17–78 (Mean = 46)	F = 63; M = 07	Azathioprine (1/50 mg/day) Corticosteroid (5/5–10 mg/day) Cyclophosphamide (2/2.5 mg/Kg/day) Infliximab (1/200 mg/every 8 weeks) Leflunomide (2/20 mg/day) Metrotexate (8/5–20 mg/week) Sulfasalazine (2/1.5–2 mg/day)
Pistone, 2010[39]	Cross-sectional	France	23	HIV (23)	12–55 (Mean = 41)	F = 10; M = 13	Unspecified antiretroviral (22/ND)
Receveur, 2000[40]	Case series	France	2	HIV (2)	34–37	F = 01; M = 01	Lamivudine (1/ND) Zidovudine (1/ND)
Scheinberg, 2010[41]	Retrospective cohort	Brazil	32	Rheumatoid arthritis (17)	Immunodepressed: 26–58 Comparison: 29–51	Imunodepressed F = 13; M = 14 Comparison = 7; M = 8	Metrotexate (12/15 mg/week) (1/17.5 mg/week) (4/20 mg/week)
Silva, 2014[42]	Case report	USA	1	Timoma/myasthenia gravis	60	F = 01	ND
Sidibe, 2012[43]	Cross-sectional	Mali	115	HIV (115)	18–65 (Mean = 35)	F = 88; M = 27	Unspecified antiretroviral (110/ND)
Stuhec, 2014[44]	Case report	Slovenia	1	Psoriatic arthritis (1)	27	M = 01	Metrotexate (1/10 mg/day)
Tattevin, 2003[45]	Cross-sectional	France	12	HIV (12)	22–50	ND	Unspecified antiretroviral (9/ ND)
Valim, 2020[46]	Prospective cohort	Brazil	278	Rheumatoid arthritis (79) Spondyloarthritis (59) Systemic sclerosis (8), Systemic lupus erythematosus (27), Sjogren's syndrome (54)	Immunodepressed: mean = 51 Comparison: mean = 56	Imunodepressed F = 163; M = 64 Comparison F = 29; M = 22	Prednisone (33/ND) Metrotexate (65/ND) Azathioprine (13/ND) Sulphasalazine (2/ND) Hydroxychloroquine (39/ND) Leflunomide (21/ND) Mycophenolate (3/ND) Cyclophosphamide (5/ND) Cyclosporine (1/NA)
Veit, 2009[47]	Cross-sectional	Switzerland	102	HIV (102)	Median: 34.7	F = 48; M = 54	Unspecified antiretroviral (41/ND)
Verdiere, 2018[48]	Retrospective cohort	France	71	HIV (40)	Immunodepressed: 25.3–56.7 (Median = 44.4) Comparison: 19.0–53.9 (Median = 35.3)	Imunodepressed F = 02; M = 38 Comparison F = 24; M = 07	ND
Yax, 2009[49]	Case report	USA	1	Bone marrow transplant (1)	62	M = 01	Glucosamine, Fluticasone, Inhaled Fluticasone (1/ND)

NA: not applicable; ND: not described; F: female; M: male.

[a]Five participants from the comparison group and one from the immunodepressed group were excluded for not attending the scheduled visits. [b]Two participants were excluded because they had been previously vaccinated against YF (one of each group) and one participant in the immunocompromised group lost their notes, making it impossible to establish adverse events. [c]Of the total sample, only seven received the YF vaccine. [d]Of the four participants, only three had data on the population of interest.

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None of the seven evaluated domains present a low risk of bias, with 60% of the domains considered at risk of critical bias, 20% at risk of severe bias and 20% at risk of moderate bias. Confounding bias was considered critical in 60% of the assessments and was the domain with the highest risk of bias. Loss to follow-up was considered low in 80% of the evaluations (Supplementary Figure S3).

YF vaccine safety

The studies included in the qualitative synthesis included 1108 participants, of which 149 immunocompromised and 85 non-immunocompromised participants had non-serious adverse events, with higher frequency of events in non-immunocompromised individuals (37.8%) compared with immunosuppressed individuals (20.4%). Fever and pain or hyperaemia at the inoculation site were the most described local adverse events, followed by headache and arthralgia/myalgia, as systemic reactions. In addition, studies described other non-serious post-vaccination adverse events, such as nausea, fatigue, asthenia, arthralgia, dizziness, anaemia, neutropenia, thrombocytopenia and elevation of liver enzymes.

Four studies described serious adverse events, two case series and two case reports Martin *et al.* (2001)[36] included three participants, who had Crohn's disease, polymyalgia rheumatica and thymoma and presented viscerotropic disease associated with the YF vaccine, followed by death and Barwick *et al.* (2004)[27] described four cases of timoma who developed viscerotropic disease associated with the YF vaccine (one followed by death).

The case report described by Silva *et al.* (2014)[42] included a woman with timoma and myasthenia gravis who developed viscerotropic disease associated with the YF vaccine, followed by death, and Kengsakul *et al.* (2002)[34] reported a case of a man with HIV who developed myelomeningoencephalitis followed by death after YF vaccination.

Thirteen studies presented data for meta-analysis. Seven studies (362 participants) were assessed by proportion meta-analysis.[26,30,38,39,43,45,47] The frequency of adverse events was 8.5% (95% CI 0.07–21.8), as presented in Supplementary Figure S4.

Due to the high heterogeneity ($I^2 = 90\%$), a subgroup analysis was performed considering the condition of immunosuppression (Figure 1). In the two studies carried out with participants undergoing transplants,[26,30] the measure of the frequency of adverse events was 2% (95% CI 0–10). The frequency of adverse events of any severity in the study carried out in participants with rheumatologic diseases[38] was 23% (95% CI 14–34). Four studies were performed in participants with HIV infection[39,43,45,47] and the frequency of adverse events was estimated to be 9% (95% CI 0–32). Both subgroup analyses used the random effects model. No other subgroup analyses were performed due to the lack of sufficient data for this approach.

The results of six cohort studies were combined to obtain a summary measure of adverse event risk (RR) due to the YF vaccine.[25,28,35,41,46,48] Faced with non-statistical heterogeneity, a fixed effects model was used ($I^2 = 0\%$), with a pooled RR equal to 1 (95% CI 0.78–1.29) (Figure 2).

Although no relevant statistical heterogeneity was identified, the included studies could potentially present diversity in terms of immunosuppression conditions, interventions and manners of conduction. Therefore, a subgroup analysis was performed to understand whether the underlying condition of the immunosuppressive state could explain the variation in the results of this meta-analysis (Figure 3). In the two studies that included participants with HIV infection[25,48] and with no detectable heterogeneity, the pooled RR was equal to 0.85 (95% CI 0.53–1.38). Four studies were carried out in participants with rheumatologic diseases or other diseases who were using immunosuppressive drugs.[28,35,41,46] Using the random effects model, the estimated RR was 1.11 (95% CI 0.84–1.47).

The methodological quality of the studies with comparator groups[25,28,35,41,46,48] was considered heterogeneous, with three studies[35,46,48] presenting a moderate risk of bias, two[28,41] presenting a severe risk of bias and one presenting a critical risk of bias.[25] Thus, a subgroup analysis was performed regarding the methodological quality (Figure 4). In the studies with the worst methodological quality,[25,28,41] there was no heterogeneity between the results, with an RR = 1.14 (95% CI 0.79–1.64), and in studies with moderate methodological quality,[35,46,48] the pooled RR was 0.95 (95% CI 0.68–1.34).

The funnel plot of the proportion meta-analysis presents symmetry in the distribution of the studies, and the Begg's test, with a $P = 0.4527$, indicates no publication bias (Supplementary Figure S5). However, the funnel plot of the risk factor meta-analysis suggests publication bias, with an asymmetry in the distribution of the studies, with studies located preferentially in the area in favour of the intervention at the bottom of the funnel; the Egger's test showed a $P = 0.2091$ and the Begg's test showed a $P = 0.1416$ (Supplementary Figure S6).

Evidence level assessment

The evidence was assessed by the GRADE tool, with the level of evidence classified as very low. The evaluated outcome was classified as critical due to its importance for the decision process. The risk of bias was considered very serious due to the inclusion of cross-sectional studies, case series and case reports, and the methodological quality of the studies assessed by the ROBINS-I tool was considered critical in most of the included studies. Inaccuracy was classified as severe due to the large amplitude of the different CIs (Supplementary Table S2).

Discussion

This systematic review was conducted with the objective of synthesizing knowledge about the risk of adverse events due to YF vaccination in immunocompromised individuals. Their results do not allow us to state that there is an association between the YF vaccine and adverse events in these individuals, regardless of the baseline condition related to immunosuppression.

The risk of adverse events after YF vaccination in immunocompromised patients was 8.5%. No data regarding this frequency were found in other publications, possibly due to the usual contraindication of using this immunobiological agent in immunocompromised individuals. In the general population, the frequency of adverse events after YF vaccination is ~4%.[50] It is noteworthy that the estimated proportion of this systematic review varied according to the evaluated group, being ~2% in

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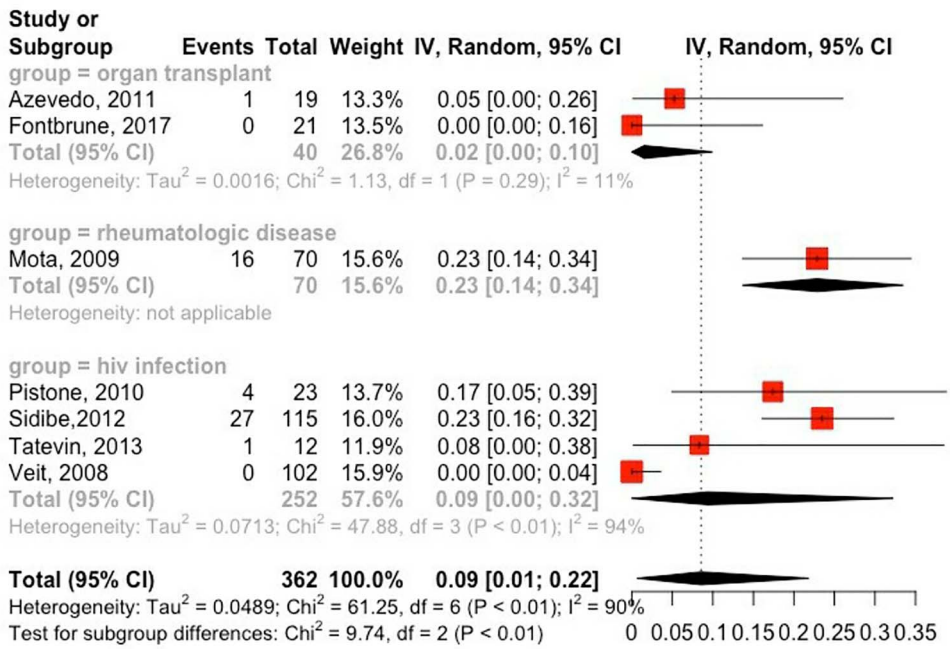

Figure 1. Forest plot of the meta-analysis of the proportion of adverse events after the use of YF vaccine by subgroups according to the immunosuppressive condition

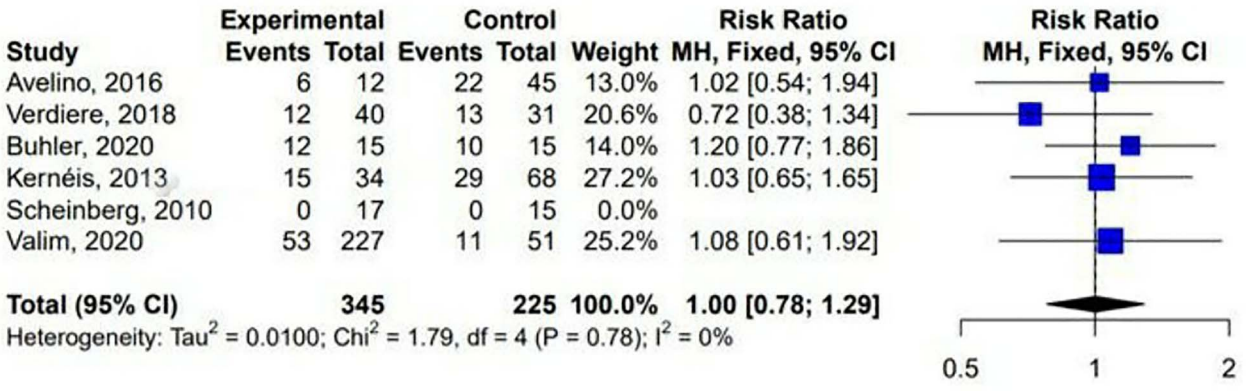

Figure 2. Forest plot of risk factor meta-analysis for adverse events after YF vaccine use in accordance with immunosupressed

individuals undergoing transplantation, 9% in participants with HIV infection and 23% in patients with rheumatologic diseases using immunosuppressive drugs. The data presented should be evaluated with caution due to the limited number of studies.

Twenty-five studies were included in this review, despite the comprehensive and sensitive search, which can be justified by the contraindication to the use of a live attenuated virus vaccine in immunocompromised patients. No studies published in languages other than Portuguese, English, Spanish and French were identified in the search and excluded.

An important limitation of this review is related to the assessment of the methodological quality of the included studies. Most studies presented a severe to critical risk of bias, which can be attributed to the nature of most of the included study designs, such as cross-sectional studies, case series and case reports. Despite this, the analysis by subgroup according to the methodological quality did not show differences in the results.

Of the 25 included studies, eight were published after the beginning of the YF outbreaks in Africa and Brazil, which determined the intensification and expansion of vaccine strategies on several continents, as well as greater attention to the vaccination of travellers.

The included studies were mostly carried out in Brazil and France. The fact that Brazil is a country with endemic YF and that its vaccination rates expanded from 2018 onwards, in addition to the headquarters of Bio-Manguinhos, one of the producers of the YF vaccine, located in Brazil, and that the headquarters of Sanofi Pasteur—Marcy l'Etoile, the manufacturer of the Stamaril® vaccine that is marketed worldwide, is located in France, may be part of the justifications for this finding.

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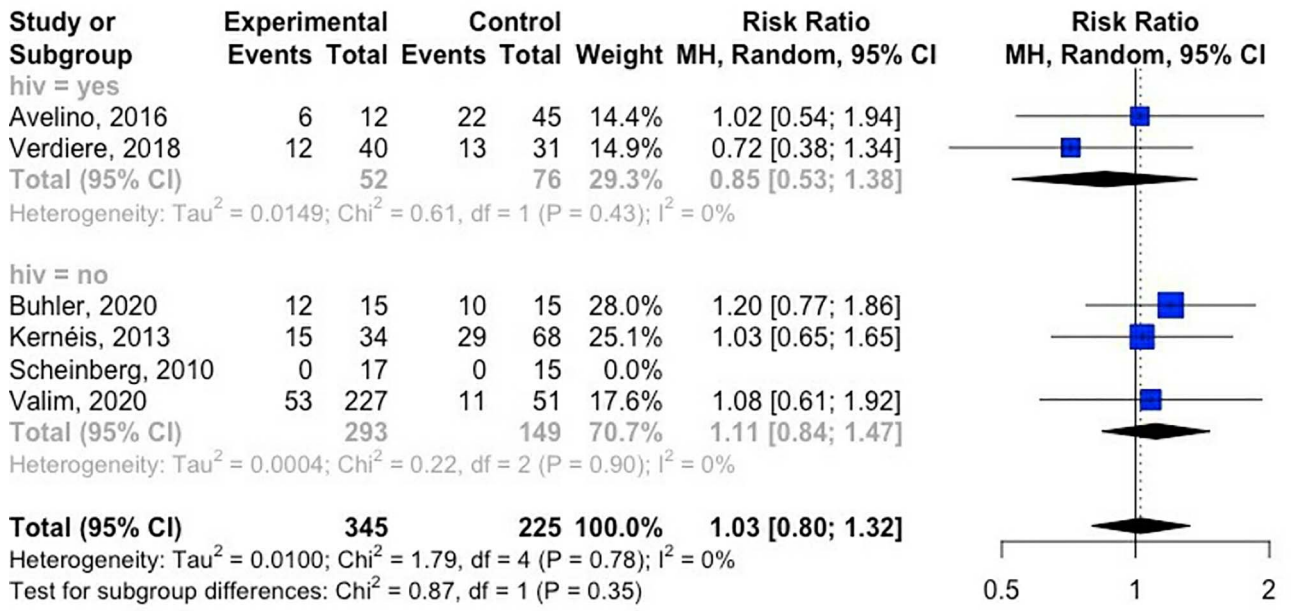

Figure 3. Forest plot of risk factor meta-analysis for adverse events after YF vaccine use in subgroups of participants with HIV infection and other causes of immunosuppression

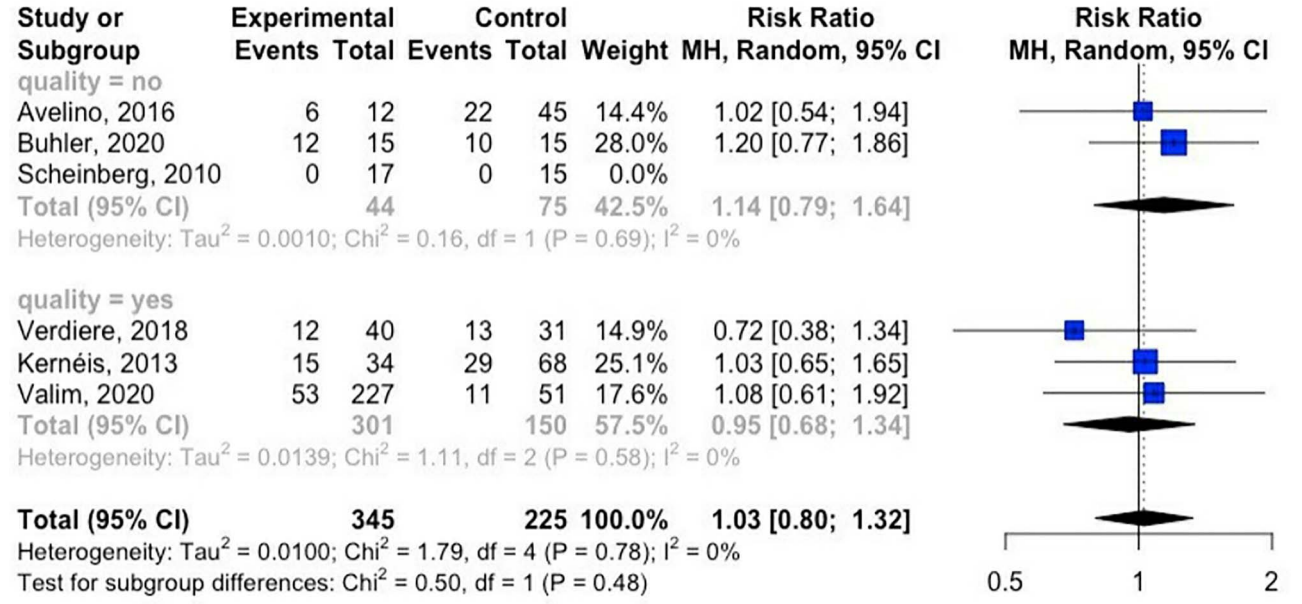

Figure 4. Forest plot of the risk factor meta-analysis for adverse events after the use of YF vaccine in participants with HIV infection or other causes of immunosuppression by subgroup according to the methodological quality of the studies

In 56% of the included studies, the YF vaccine was given to travellers to endemic areas, as recommended by the WHO,[51] which may justify the inclusion of studies carried out in developed countries such as France, the USA, Switzerland, Denmark, the UK and Slovenia. Only one study was carried out on the African continent (in Mali, involving 115 individuals with HIV), an endemic area for YF, reinforcing the need to conduct studies in populations in this region.

Most studies did not report the coadministration of vaccines. To date, there is no scientific evidence that the immune system is overloaded with the simultaneous administration of different vaccines, making it safe and effective to use this practice.[8] Although the coadministration of vaccines can make it difficult to interpret some adverse events, there are known examples of serious adverse events specifically associated with the YF vaccine, such as YF vaccine-associated neurological disease and YF vaccine-associated viscerotropic disease, which are not associated with other immunobiologicals.[52]

According to the WHO, post-vaccination adverse events are any serious, unexpected or undesirable signs or symptoms that

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occur after vaccination. These signs and symptoms may be associated with the vaccine and occur due to vaccination or the association may only be temporal, without a causal link.[53] This review identified only eight cases of serious adverse events; in two of them, the YF vaccine strain was identified in the blood of the individuals through laboratory methods, and it was possible to attribute the serious adverse event to the YF vaccine.

The most common local adverse events identified in the included studies were pain and hyperaemia at the inoculation site, and among the general manifestations, the most described symptoms were fever, headache, myalgia and arthralgia. However, mild local or systemic symptoms do not require mandatory notifications and are often much more underreported than severe symptoms. Thus, the frequency measure that is obtained may be below the prevalence of these events.

Immunosuppression has heterogeneous aetiologies and is characterized by quantitative and/or qualitative deficiencies in cellular and humorall immunity with varying degrees of severity. The level of immunosuppression is difficult to quantify, varying according to the drug doses, combination therapy and duration of immunosuppression.[54] In addition, the included studies did not consistently provide data on immunosuppressive drugs and their doses, making their correlation with adverse events due to the YF vaccine difficult, and this information is of paramount importance.

Recently, a study described a possible mechanism that explains worse outcomes after the YF vaccine in individuals, including immunocompromised patients. According to the authors, auto-Abs act by blocking the protective effect of IFN-α2 against YF vaccine strains. Furthermore, deficiency of IFNAR1 or IFNAR2 AR and auto-Abs against type I IFNs may be associated with serious events associated with vaccination.[55] Another important point refers to the small number of studies included in the meta-analyses to identify publication bias. The Begg's and Egger's tests have limitations in the assessment of this bias when there are few studies in the meta-analysis ($n < 10$).[56]

The quality of evidence according to the GRADE tool was classified as very low. The confidence in the effect estimate is very limited, with a significant degree of uncertainty in the findings.[23]

A limitation of the study refers to the fallacy of the base rate in the calculation of the RR of adverse events after YF vaccination when comparing immunocompromised with non-immunocompromised individual, because due to the risk after vaccination, immunosuppressed individuals are less vaccinated.

The success of immunization programs creates a controversial situation; as vaccination advances and reduces the risk of vaccine-preventable diseases, fears of adverse events after vaccination increase, which can lead to a decrease in vaccinations, allowing the resurgence of controlled diseases. Therefore, studies with methodological rigour and with a larger sample size are needed to create assertive vaccination strategies for this population, which is more vulnerable to contagious infectious diseases. In addition, it is important that data such as the therapeutic regimen of the immunosuppressants used, the dose and vaccination schedule (first vaccination or booster) and specification of adverse events are described, so that it is possible to recognize relationships between these aspects, the underlying pathologies and the reported adverse events.

Conclusions

The use of the YF vaccine in immunocompromised patients with an increased risk for adverse events is a controversial issue considering the limited evidence regarding safety thus far. Conducting this systematic review was important because it involved a comprehensive and up to date search, including diverse populations of immunocompromised individuals.

Although rare, there is a potential risk of replication of the attenuated vaccine strain in immunocompromised individuals, leading to serious adverse events, such as viscerotropic or neurotropic disease, and death. The presented results do not allow us to affirm that immunocompromised individuals are at an increased risk of adverse events due to YF vaccination when compared with non-immunocompromised individuals. In view of these findings, it is important that physicians and decision-makers carefully assess the use of the YF vaccine in immunocompromised patients.

Supplementary data

Supplementary data are available at *JTM* online.

Author Contributions

L.W.A.L. contributed to literature search; L.W.A.L. and A.J.L.A. contributed to selection of the studies, data extraction and quality assessment; L.W.A.L., R.C., J.U.B. contributed to data analysis; L.W.A.L. drafted the article and all authors read and commented on the final draft.

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Conflict of interest

None declared.

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