Risk of yellow fever vaccine-associated viscerotropic disease among the elderly: systematic review

Ellen Rafferty[A,1] , Philippe Duclos[B], Sergio Yactayo[B,2] , Melanie Schuster[B].

[A]University of Saskatchewan, Saskatoon, Saskatchewan S7N 5A2

[B]World Health Organization, 20 Ave Appia, CH-1211 Geneva 27, Switzerland

Three of the authors are World Health Organization staff members. The opinions expressed in this article are those of the authors and do not necessarily represent the decisions, official policy or opinions of the World Health Organization.

[1] Current Address: 247 Edgemont Pl NW, Calgary, AB, T3A 2K1, Canada

[2] Corresponding Author: tel: +41227911346, fax: 41227914198, email address: yactayos@who.int

Abstract:

Yellow fever vaccine-associated viscerotropic disease (YEL-AVD) is a rare and serious adverse event of the yellow fever (YF) vaccine that mimics wild-type YF. Research shows there may be an increased risk of YEL-AVD among the elderly population (>60), however this research has yet to be accumulated and reviewed in order to make policy recommendations to countries currently administering the YF vaccine. This paper systematically reviewed all information available on YEL-AVD to determine if there is an increased risk among the elderly, for both travelers and endemic populations. Age-specific reporting rates (RRs) were re-calculated from the literature using the Brighton Collaboration case definition for YEL-AVD and were then analyzed to determine if there was a significant difference between the RRs of younger and older age groups. Two out of the five studies found a significantly higher rate of YEL-AVD among the elderly population. Our findings suggest unexposed elders may be at an increased risk of developing YEF-AVD, however the evidence remains limited. At the same time, an older population's experience with YF and YF vaccine (e.g. how many primo vaccine recipients they have? What is their risk of developing YF?) should be taken into consideration when judging the risk of administering the YF vaccine.

Keywords: Yellow fever, yellow fever vaccine, adverse event, viscerotropic disease among elderly.

Abbreviations: YF, yellow fever; YEL-AVD, yellow fever vaccine-associated viscerotropic disease; RR, reporting rates; RRR, reporting rate ratios; AVD, viscerotropic disease; AEFI, adverse events following immunization; YFWG, yellow fever vaccine safety working group.

1. Introduction

Yellow fever (YF) is a mosquito-borne disease that is endemic in South Central America and sub-Saharan Africa [1]. Fatality rates of YF vary considerably, although research from West African patients with jaundice suggest it is approximately 20% [1]. Current YF vaccines are manufactured using live attenuated YF virus sub-strains, 17DD and 17D-204 [1]. Generally, two distinct groups receive the YF vaccine, individuals traveling to countries where YF is endemic (travelers) and those who live in countries where YF is endemic or is intermittently epidemic (endemic populations).

Serious adverse events following immunization (serious AEFI) associated with the YF vaccine include viscerotropic disease, neurologic (e.g. encephalitis or acute disseminated encephalomyelitis), and severe hypersensivity reactions (e.g. anaphylaxis). Yellow fever vaccine-associated viscerotropic disease (YEL-AVD) is characterised by acute multiple organ system dysfunction due to vaccine virus proliferation [2]. In 2001, the first series of cases of YEL-AVD were reported [2]. Since then, retrospective testing has identified a case of YEL-AVD as early as 1975 [3]. YEL-AVD has a high case fatality rate, with more than 60% of reported cases being fatal [4]. To date, YEL-AVD has only been recognized in in primary vaccine recipients [4].

Laboratory tests can identify YEL-AVD by detecting vaccine strain 17D in the blood and/or the tissue of those infected, through virus cultures and viral RNA amplification [2]. In endemic settings, however, it can be difficult to differentiate between YEL-AVD and wild-type YF, primarily due to suboptimal samples and the limited availability of lab tests [1].

Until May 2012 the "main case definition" used for YEL-AVD was created by an informal yellow fever vaccine safety working group (YFWG). The YFWG was convened by the Centers for Disease Control and Prevention (CDC) in the US and consisted of a wide range of YF experts. The YFWG case definition was originally created in 2002 and updated in 2008. However, it was never subjected to the formal peer review process and was never accepted as the global standard [1-2]. In 2012, the Brighton Collaboration Viscerotropic Disease WG (Brighton WG) published a standardized case definition for viscerotropic disease, as well as guidelines for classifying, analysing and presenting information related to these cases [1].

The Brighton WG case definition of AVD outlines three levels of diagnostic certainty, with Level 1 having the highest specificity [2]. Each case of viscerotropic disease can then be categorised into one of the three levels of diagnostic certainty based on the presence of major and minor criteria. Cases that do not meet the requirements for one of the three levels of diagnostic certainty are classified as having 'insufficient evidence' [2]. The Brighton WG also developed a causality algorithm to assess the association with the YF vaccine; this algorithm was included as an appendix to the case definition. [2]. There are four categories of causality, Definite, Probable, Suspected or Insufficient evidence [2]. The determination of causality into one of these categories is primarily based on the isolation and/or amplification of 17D virus or 17D RNA from the blood or tissue of the infected RNA [2].

Studies suggest that there is a higher risk of serious adverse events following YF vaccination (YF-AEFI), in particular for YEL-AVD, among the elderly. [5-9]. These studies primarily use age-specific reporting rates (RRs) and reporting rate ratios (RRRs) as proxies for determining risk in the elderly population [5-9]. However, researchers have never systematically reviewed the methodology, populations and generalisation of these studies. A recently published systematic review on the safety of YF vaccine in high risk groups, including the elderly, simply restated the conclusion of the previous studies without utilizing a uniform case definition or more specifically using the updated Brighton case definition for viscerotropic disease [10]. Therefore, the objective of this review is to re-calculate the current risk of YEL-AVD (using the Brighton Collaboration case definition) among the elderly for both travelers and endemic populations.

2. Methods:

2.1. Overview:

This review uses 3 steps to determine the risk of YEL-AVD among the elderly:

1. Identify, classify (Brighton Classification- diagnostic certainty and causality), and categorise by age, all published cases of YEL-AVD.

2. Identify and review articles identifying advanced age as a risk factor for YEL-AVD in travelers and critically analyse their methodology. Including, re-calculation of RRs and RRRs using the Brighton Classification.
3. Identify and review articles concerning advanced age as a risk factor for YEL-AVD in endemic populations and identify general RRs of YEL-AVDs in endemic populations to estimate the risk in this group.

2.2. Search Method:

This systematic review primarily builds on the work of Thomas et al. (2012), as a starting point for the literature search [10]. In their review, Thomas et al. (2012) searched nine databases, all languages, no date limits and up until December 2010 [10]. The databases searched included the Cochrane Library (Cochrane CENTRAL Register of Controlled Trials, the Cochrane Database of Systematic Reviews and the NHS Database of Abstracts of Reviews of Effects (DARE)), MEDLINE (OVID 1950 to present), EMBASE (OVID 1910 to present), BIOSIS [10]. After duplicates were removed, all abstracts were read by two independent reviewers [10]. Articles were included if they had data on the risk factors (e.g. pregnancy, elderly, HIV+) associated with serious AEFI with YF vaccine [10].

We also identified articles through an up-dated literature search modeled on Thomas et al. (2012). This literature search included articles from two databases (Pubmed and MEDLINE (OVID 1950 to present)), published between December 2010 and May 2012, and in all languages. Furthermore, articles were obtained from additional sources, including scanning the reference lists of included articles for relevant studies and receiving articles from YF experts who had access to additional and pre-published sources.

After removing any duplicates, we screened all the articles' titles and abstracts for inclusion and exclusion based on specific criteria. We excluded any literature reviews, non-research letters, articles relating to a specific population other than the elderly (e.g. HIV+ patients) and any article prior to 2001. We excluded any article prior to 2001 as YEL-AVD was first described in 2001 [1]. We included any article that had YEL-AVD case-specific information, RRs of YF-AEFI among the elderly and general RRs of YF-AEFI in endemic populations. Subsequently, we reviewed the full-text of all remaining articles. We included articles in the final systematic review based on the above inclusion/exclusion criteria, as well as their relevance to the three method areas outlined at the beginning of the Methods section (*2.1. Overview*).

2.3. Statistical Methods

Age-specific RRs were re-calculated using the number of confirmed reports of YEL-AVD that fit the level of diagnostic certainty (Level 1, 2, 3) in that age-group as the numerator, and the number of doses of YF vaccine given to that age group as the denominator. Denominators were drawn directly from the original articles and were generally based on doses of YF vaccine sold, as well as surveys to determine the age distribution of YF vaccinations (e.g. travel clinic, general practices statistics) [5-9]. Age-specific RRs were also re-calculated using the number of cases of YEL-

AVD that fit the causality algorithm (Definite, Probable, Suspected) as the numerator, compared to the same denominator. As in the original articles, the re-calculated RRs were considered as a proxy for the true risk of developing YEL-AVD.

RRRs and 95% confidence intervals (CI) were calculated with the Taylor Series statistical analysis using OpenEpi software. All RRRs were calculated by taking the new RRs (as calculated above) of the younger age group (e.g. <60) as a reference population and comparing it to the new RRs of the elderly population (e.g ≥60). The 95% CI were then used to determine if there was a significant difference between the RRs of the reference population and the elderly population.

2.4 Scoring of the quality of evidence

For scoring of the evidence on Yellow Fever- AVD in elderly, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology was used. GRADE functions as a tool to support the process of evidence-based decision making and is used by WHO and other large organizations. The outcome of the grading and along with supplementary criteria, such as ethical aspects, cost-benefit and/or burden of disease considerations, allows panels to make evidence-based recommendations. Further information on GRADE can be found on the WHO website: http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf

In regard to this review, two questions were considered for grading: the risk of Yellow Fever AVD in elderly travelers and the risk of Yellow Fever AVD in elderly in an endemic population.

4. Results

4.1. Literature search:

We identified 529 articles, 101 of which were selected for full-text review based on their titles and abstracts. Of those, 33 articles were included in the final systematic review. Twenty-four articles provided information on specific cases (two of which also included information on general RRs), five on advanced age as a risk factor for YEL-AVD among travelers (age-specific RRs), one on age-specific RRs within endemic populations and five on general RRs within endemic populations (See Fig. 1)

4.2. Classification of Cases

After applying the Brighton Classification for diagnostic certainty and causality to specific YEL-AVD cases, the distribution and number of cases changed. See Table 1a and Table 1b.

4.3. Risk in elderly travelers

Five articles studied the risk of YEL-AVD in the elderly traveler population [5-9] See Table 2. All five articles estimated risk of serious AEFI by calculating age-specific RRs of YEL-AVD, and four also calculated RRRs. All five articles were

retrospective studies, where the authors found cases of serious AEFI in an immunisation adverse event databases, for example in the Vaccine Adverse Event Reporting System (VAERS) in the US. Some of the YEL-AVD cases from these articles overlap, specifically, Martin et al. (2001) and Khromava et al.'s (2005) US cases overlap from 1990-1998, and Khromava et al. (2005) and Lindsey et al.'s (2008) US cases overlap from 2000-2002 [5-6,9]. Authors used a variety of methods to determine the age distribution of YF vaccinations, including surveys of travel clinics and statistics taken from physicians' general practices. For example, both Martin et al. (2001) and Khromava et al. (2005) used a 1998 survey of thirteen US travel clinics to determine the age distribution of YF vaccines [6,9]. All five articles concluded that there was an increased risk of serious AEFI, including YEF-AVD, from YF vaccination among the elderly.

We were able to re-calculate the RRs and therefore RRRs for three out of the five articles using only cases of YEL-AVD (rather than all serious AEFI) and applying the Brighton Classification of diagnostic certainty and causality (Table 2). In two articles, new age-specific RRs could not be calculated due to lack of information about the specific YEL-AVD cases [5,7]. RRs fell in nearly all age groups, with the greatest difference in the ≥60 population. The re-calculated RRRs for Martin et al. (2001) and Khromava et al. (2005), comparing elders (≥65 and ≥ 60 respectively) to the reference population, stayed high, and were significantly higher in three out of four re-calculations. However, in the Lawrence et al. (2004) paper the RRs dropped and the RRRs were not significant [8].

4.4. Risk in endemic populations

Seven articles calculated general RRs in endemic populations (Table 3) [17, 31-36]. de Menezes Martins et al. (2010) was the only article to calculate age-specific rates of YEL-AVD within an endemic population (i.e. Brazil) [33]. We were unable to re-calculate RRs as case specific information was not provided. de Menezes Martins et al. (2010) reported the highest RRs were among the three (0.053 per 100 000) and four year olds (0.098 per 100 000) [33]. The RR of the ≥60 age group (0.043 per 100 000) was above the average (0.019 per 100 000) [33]. However, when we calculated the RRR and compared ≥60 to a reference population (15-59yrs), it showed no significant difference [RRR=2.57, 95% CI (0.566, 8.536)]. We were unable to re-calculate RRs as case specific information was not provided. For all articles, the RRs for endemic populations were small. However, there is one outlier, Peru, that had a lot-specific RR of 11.7 per 100 000 [17, 34]. The cases of YEL-AVD in these studies ranged in age from 4-79 years old, and there did not appear to be an increase in reports among the elderly population.

4.5.Scoring of the quality of evidence

Grading of the quality of evidence showed age-related tendencies among those that received the YF vaccine; specifically there was some evidence of higher rates of serious AEFI among elderly. Furthermore, this association could be seen in endemic populations, as well as traveling populations. However, confidence in the estimate of the effects is limited and further research is need to support these hypotheses. The complete GRADE tables can be accessed on the WHO website: http://www.who.int/immunization/documents/positionpapers/en/index.html

5. Discussion

Overall, we found that the crude number of reported cases of YEL-AVD among the elderly (>60) that met the case definition or the causality algorithm was quite high ($n_{\geq 60}$= 14) compared to all the other age groups combined ($n_{<60}$= 17). Furthermore, our analysis supported an increased risk of YEL-AVD among the elderly, particularly elderly travelers, however this evidence may be weaker than originally thought. After applying the Brighton Classification for both diagnostic certainty criteria and causality, the re-calculated RRs for Martin et al. (2001) and Khromava et al. (2005) remained the highest among the oldest age group, ≥70 and ≥75 respectively [6,9]. In addition, the re-calculated RRRs for these studies remained statistically higher in the older populations, ≥ 65 and ≥60 respectively [6,9]. These results demonstrate that the RR of YEL-AVD in the elderly population was significantly higher than the RR in the reference population. However, these two studies did include some overlap in the cases considered and thus may not represent independent proof of a higher risk of YEL-AVD among elderly travelers [6,9]. In contrast, the re-calculated RRs for Lawrence et al. (2004) were the highest in the 45-65 age group, rather than the ≥65 age group, and their RRR very low as there were no cases in the ≥65 age group [8]. This may be due to the small sample size of the ≥ 65 group (n=8,984) [8]. The other two articles, Lindsey et al. (2008) and Monath et al. (2005) did not provide sufficient information to calculate the risk.

Recently, Roukens et al (2012) documented more frequent viraemia with a higher YF vaccine RNA copy numbers in elderly than in younger naïve vaccine recipients [37]. According to Roukens et al (2012) the elderly also had a delayed antibody response to the YF vaccine [37]. The authors hypothesized that slower antibody response and increase in viraemia may lead to an increased risk of developing serious AEFI, such as YEL-AVD, and therefore could explain the higher rates of serious AEFI in the elder population [37].

There is only one published article that calculates age-specific RRs of YEL-AVD in an endemic country [33]. Although this study does demonstrate a slightly higher RR of YEL-AVD among the elderly than the average RR, de Menezes Martins et al. (2010) did not calculate whether it was *significantly* higher than the average [33]. In fact, when we calculated the RRR and compared ≥60 to a reference population (15-59yrs), it showed no significant difference. The report also noted the case fatality rate was 92.3% for YEL-AVD cases. This case fatality rate is higher than the 60% noted in a more systematic review of YEL-AVD cases and suggests a possible bias in how cases were collected [33].

Based on the studies dealing with RRs in endemic countries [17, 31-36] (Table 3), the rate of YEL-AVD in these populations is generally quite low. Moreover, after applying the Brighton Classification there were very few cases in the elderly endemic population ($n_{\geq 65}$=1). Previous studies postulate that the difference in rates of YEL-AVD in traveling and endemic populations is because there are fewer primo-vaccine recipients in the older population of endemic countries [4]. Primo-vaccine recipients often become viraemic following vaccination. Conversely, viraemia has not been documented in persons receiving a booster dose of YF vaccine.

There are other potential reasons for the difference in rates between traveling and endemic populations that make it difficult to compare these two

groups. For example, the diverse forms of vaccine administration (i.e. general practitioner or travel clinics versus national mass immunizations campaigns) signify there are various ways for measuring denominators in the two populations [38]. Furthermore, the methods of YEL-AVD case finding are diverse in the two populations and are dependent on knowledge about YEF-AVD among healthcare providers, surveillance systems to detect and record information on cases, and having adequate laboratory capacity to assess the level of certainty of a case (e.g. liver enzyme tests, clotting tests) and YF vaccine causality. These diverse methods of case finding and denominator determination often lead to the underestimation of RRs of YEL-AVD in endemic countries.

There are multiple methodological limitations in the studies used to determine the risk in the elderly population. One of the foremost issues relates to problems with the populations and denominators the authors used. For example, both Martin et al. (2001) and Khromava et al. (2005) determined the age distribution for the RR denominators from a 1998 survey of 13 travel clinics [6,9]. This survey used a very small and particular sample of the population which may have resulted in biases; for instance elderly persons may have been less likely to attend travel clinics to receive their YF immunisations [6,9]. In addition, this study was out of date for Khromava et al. (2005) who studied cases of YEL-AVDs up until 2002 [9]. Furthermore, Martin et al. (2001) did not study the rates of YEL-AVD for anyone under 15 [6]. The limitations of these studies are important to note because they may impact our ability to draw conclusions from the data from these studies.

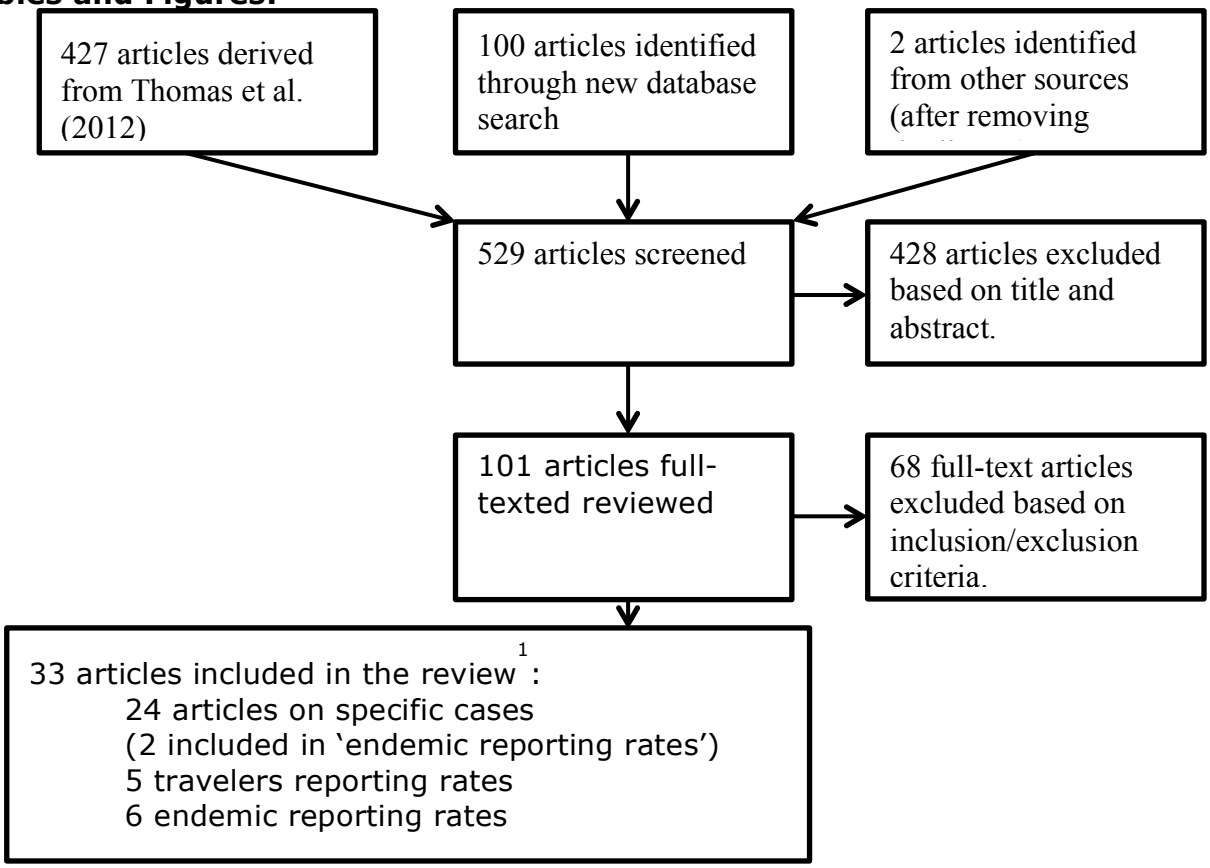
This systematic review has several other limitations. First, the primary use of another systematic review as the basis for article-finding and information-gathering may be considered a less rigorous method of gathering the literature. The updated literature search was not as broad or as systematic as previous searches (i.e. only two databases, only one article reviewer). Second, the lack of primary case data prevented reclassification of several cases and may have led to the incorrect classification of some cases using Brighton case definition. Third, endemic countries often do not possess the ability to perform more complicated diagnosis and investigatory laboratory test, making appropriate classification of these cases difficult. Fourth, the variable age-groups in the studies on YEL-AVD make it difficult to compare studies, and therefore difficult to determine the ultimate risk of YEL-AVD for elderly populations.

Research needs to continue to study advance age as a risk factor for YEL-AVD, especially in endemic countries. Moreover, research must continue to monitor YF-AEFI, particularly YEL-AVD in both national campaigns and through surveillance systems (e.g. VAERS). Finally, it is essential the Brighton Classification for viscerotropic disease, including the level of diagnostic certainty and causality algorithm, becomes the international standard for determining and describing YEL-AVD. This international standard would allow countries to understand and develop the required tests to appropriately classify a case of YEL-AVD, as well as allow comparison rates of YEL-AVD in diverse countries and settings.

In summary, our findings suggest there may be an increased risk of YEF-AVD among unexposed elders (i.e. travelers). At the same time, older populations' experience with YF and YF vaccine should be taken into consideration when judging the risk of administering the YF vaccine. For example, the risk of contracting YF is significantly higher for individuals in endemic populations who are often exposed to

YF for much longer time periods than travelers. Furthermore, as stated earlier, many of those among the elderly population in endemic countries are not primary vaccine recipients or yellow fever naïve and therefore do not have the same risk of developing YEL-AVD.

Tables and Figures:



[1] 30-articles from Thomas et al. (2012), 2-articles updated literature search, 1- article from other sources

Fig. 1. Search results flow diagram

Table 1a
Classification of YEL-AVD cases

YEL-AVD	Location	Brighton collaboration	
		Diagnostic Certainty	**Diagnostic Causality**
Number of YEL-AVD cases (n=47) [1, 3, 11-32]	**Travelers (n=28, 59.6%)** (i.e. US, Australia, Belgium, Switzerland, Germany, France, Spain, Wales, Japan and China) **Endemic (n=19, 40.4%)** (Brazil, Peru, Ecuador, and Columbia).	**Level 1 (n=17, 36.2%)** [1, 12, 13, 15-17, 20-22, 24, 25, 27, 28] **Level 2 (n=7, 14.9%)** [1, 14, 21, 25, 31] **Level 3 (n=6, 12.8%)** [1, 17, 18, 21, 23, 25, 29, 31] **Insufficient data (n=17, 36.2%)** [1, 3, 19, 23, 26, 30, 32]	**Definite (n=12, 25.5%)** [12-14, 16, 17, 21, 22, 25, 27, 28, 31] **Probable (n=5, 10.6%)** [1, 3, 15, 24, 29, 30] **Suspected (n=2, 4.3%)** [17, 24] **Insufficient data (n=28, 59.6%)** [1, 17-20, 23, 24, 26, 32]

Table 1b
Number of YEL-AVD cases by diagnostic certainty/causality and age group

Age Group	Travelers			Endemic			Total Both Brighton	Total Either[4]	Total Reported
	Both[1]	One[2]	Neither[3]	Both	One	Neither			
0-9	-	-	-	2	-	-	2	2	2
10-19	-	-	-	1	2	1	1	3	4
20-29	3	1	-	3	-	1	6	7	8
30-39	-	-	-	-	-	1	0	0	1
40-49	-	1	-	1	1	2	1	3	5
50-59	1	1	2		-		1	2	4
60-69	3	6	2	1	-	1	4	10	13
70+	1	2	2	1	-	-	2	4	6

[1]Both= met both diagnostic criteria (any level) AND causality (any level)
[2]One= met either diagnostic criteria (any level) OR causality (any level)
[3]Neither= met neither diagnostic criteria (any level) OR causality (any level)
[4]Total either= met either a level of diagnosis certainty or a classification of causality

Table 2

Articles on risk of serious YEL-AVD in the elderly traveler- General comments and re-calculated RRs/RRs

Reference	Pop	Cases (YEL-AVD)	Comments	Original RRs (reports /100 000)	New RRs Diagnostic criteria	RRRs Diagnostic criteria	New RRs Causality	RRRs Causality
Martin et al. (2001)	USA 1990-1998	YEL-AVD (n=4)	-Did not study < 15 years old. -Age-specific RRs denominator: GeoSentinel Survey of 13 travel clinics from 1998 (YF vaccine doses per age-group). -Overlaps with Khromava et al. (2005).	SAEFI 15-24=1.05 25-44= 0.29 45-64=1.13 65-74= 3.48 75+= 9.06	15-24= 0 25-44= 0 45-64= 0.23 65-74= 1.16 75+= 9.06	15-64=Ref (n=1 335 379) **≥65= 36.99 (3.45, 355.5) SIG.**[1] (n= 108 307)	15-24= 0 25-44= 0 45-64= 0.23 65-74= 0 75+= 4.53	15-64=Ref (n= 1 335 379) **≥65= 12.3 (0.77, 197.1) NOT SIG.** (n= 108 307)
Khromava et al. (2005)	USA 1990-2002	YEL-AVD (n=7)	-GeoSentinel Survey of 13 travel clinics from 1998 (YF vaccine doses per age-group). -Children underrepresented and age distribution changed over time. - Overlaps with Martin et al.(2001) and Lindsey et al. (2008).	YEL-AVD: 1-18= 0 19-29= 0.2 30-39= 0 40-49= 0 50-59= 0.3 60-69= 1.1 70+= 3.2	1-18= 0 19-29= 0.23 30-39= 0 40-49= 0 50-59= 0 60-69= 1.6 70+= 3.2	<60=Ref (n= 1 948 325) **≥60= 34.49 (4.03, 295.2) SIG.** (n= 282 435)	1-18= 0 19-29= 0 30-39= 0 40-49= 0 50-59= .31 60-69= 0.53 70+= 1.07	<60= Ref (n= 1 948 325) **≥60= 13.8 (1.25, 152) SIG.** (n= 282 435)
Lawrence et al. (2004)	Australia 1993-2002	YEL-AVD (n=1)	-Only 1 case of YEL-AVD. -Sampled travel clinics (15% of YF vaccine sales). -Small samples size in ≥65.	SAEFI: 15-24= 0 25-44=2.49 45-64=8.21 ≥65=22.26	15-24= 0 25-44=0 45-64=2.05 ≥65=0	<65= Ref (n= 201 672) **≥65= 2.04 (0.003, 1321) NOT SIG.** (n=8 984)	15-24= 0 25-44=0 45-64=2.05 ≥65=0	<65= Ref (n= 201 672) **≥65= 2.04 (0.003, 132) NOT SIG** (n= 8 984)
Monath et al. (2005)	UK 1995-1999	YEL-AVD (n=?)	-Not all case met the necessary criteria to be defined as serious AEFI. -Serious AEFI in 2 YF vaccine clinical trials (no cases of YEL-AVD) and in large general practice data base.	SAEFI: <15= 0 15-25= 2.09 25-44= 3.05 45-64= 5.55 65-74=8.58 >75= 0	N/A[2]	N/A	N/A	N/A
Lindsey et al. (2008)	USA 2000-2006	YEL-AVD (n=6)	-Low response rate. -Overlaps with Khromava et al. (2005).	YEL-AVD: ≤18= 1.1 19-29=0.3 30-39= 0.5 40-49=0.9 50-59=0.4 60-69=1.6 70+= 2.3	N/A	N/A	N/A	N/A

[1]SIG= The result is statistically significant

[2]N/A=Not enough information for the calculation

Table 3:
Articles on risk of serious YEL-AVD in endemic populations- Age-specific RRs, general RRs and general comments

Reference	Population	RRs (YF AVD reports/100 000)	New RRs (YF AVD reports/100 000)	Age-specific RR (YEL-AVD reports/100 000 doses)	Comments (RRR-95% CI)
De Menezes Martins et al. (2010)	Brazil, 1999-2009	0.019	N/A	<1= 0 1= 0 2= 0 3= 0.053 4= 0.098 5-9= 0.018 10-14= 0.017 15-59= 0.019 ≥60= 0.047	-Denominator: Brazilian Ministry of Health info on number of YFV doses administered by age. -No information given regarding case classification. -Rates are low. -Case fatality was 92.3% suggesting reporting bias. RRR (95% CI) 15-59= reference **≥60= 2.527 (0.5662, 8.536) (NOT SIG.)**
Fitzner et al. (2004)	Ivory coast, 2001	0 (2.6 million)	0	N/A	-8 suspected vaccine -associated cases ruled out based on blood sample.
Struchiner et al. (2004)	Brazil, 1991-2001 1998-2001	9 different scenarios, RRs ranging from 0.0056 to 0.213	N/A	N/A	-Four fatal adverse events in Brazil -2 YEL-AVD cases, Female-19 and Male-4, both Level 1 and Definite -Calculate different RRs based on all possible denominators.
Belmusto-worn et al. (2005)	Peru, no year	0 (n= 1107)	0	N/A	-No Serious AEFIs.
PAHO/WHO and Whittembury et al. (2009)	Peru, 2007	Total RR: 7.9 (n= 63 174) Lot specific RR: 11.7 (n= 42 742)	Total RR: 6.3 per 100 000 Lot specific RR: 9.4	N/A	-First space-time cluster of YEL-AVD with more than two cases. -High RR, generally considered an outlier. -Ages range from 23-79.
Breugelmans et al. (Prior to print)	Benin, Cameroon, Liberia, Mali, Senegal, Sierra Leone 2007	Total RR: 0.013 (n= 38 million, 5 cases, 3 suspected, 2 unclassified) Suspected cases RR: 0.08	N/A	N/A	-22 cases of serious AEFI, mean age= 23. -5 cases classified as YEL-AVD: -2 insufficient evidence (Male-15, Male-38) -3 suspected (Male-34, Female-40, ?)

Acknowledgements

We would like to thank Dr. Erin Staples (CDC Fort Collins) and Dr. Olivier Ronveaux (WHO) for reviewing the final systematic review, and providing valuable comments and advice.

We would also like to thank both Dr. Oyewale Tomori (Chair YF Working Group) and Dr. Patrick Zuber (WHO) offering advice on the conclusions of the systematic review following the YF Working Group face-to-face meeting in January 2013.

Finally we would like to acknowledge Véronique Millot for her administrative support in communication and retrieval of essential documents throughout the development of this systematic review.

References

[1] Monath T, Cetron M.S., & Teuwen DE. Yellow fever vaccine. In : Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. 5th ed. Philadelphia, PA: Saunders Elsevier, 2008. p.959-1055.
[2] Gershman MD, Staples JE, Bentsi-Enchill AD, Breugelmans JG, Brito GS, BastosCamacho LA, et al. Viscerotropic disease: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2012; 30: 5038-5058.
[3] Engel AR, Vasconcelos PFC, McArthur MA, & Barrett ADT. Characterization of a viscerotropic yellow fever vaccine variant from a patient in Brazil. Vaccine 2006;24:2803-2809.
[4] Centers for Disease Control and Prevention (CDC). Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2010;59(RR-7):1-27.
[5] Lindsey NP, Schroeder BA, Miller ER, Braun MM, Hinckley AF, Marano N, et al. Adverse event reports following yellow fever vaccination. Vaccine 2008;26:6077-6087.
[6] Martin M, Weld LH, Tsai TF, Mootrey GT, Chen RT, Niu M, et al. Advanced age a risk factor for illness temporally associated with yellow fever vaccination. Emerg Infect Dis 2001; 7(6): 945-51.
[7] Monath TP, Cetron MS, McCarthy K, Nichols R, Archambault WT, Weld L, et al. Yellow fever 17D vaccine safety and immunogenicity in the elderly. Hum Vaccin 2005; 1(5):207-14.
[8] Lawrence GL, Burgess MA, Kass RB. Age-related risk of adverse events following yellow fever vaccination in Australia. Commun Dis Intell 2004;28(2):244-8.
[9] Khromava AY, Eidex RB, Weld LH, Kohl KS, Bradshaw RD, Chen RT, et al. Yellow fever vaccine: An updated assessment of advanced age as a risk factor for serious adverse events. Vaccine 2005; 23(25):3256-63.
[10] Thomas RE, Lorenzetti DL, Spragins W, Jackson D & Williamson T. The safety of yellow fever vaccine 17D or 17DD in children, pregnant women, HIV+ individuals, and older persons: Systematic Review. Am J Tro Med Hyg 2012;86(2):359-372.
[11] Bae H, Domingo C, Tenorio A, de Ory F, Muñoz J, Weber P, et al. Immune response during adverse events after 17D-derived yellow fever vaccination in Europe. J Infect Dis 2008; 197(11): 1577-84.
[12] Belsher JL, Gay P, Brinton M, DellaValla J, Ridenour R, Lanciotti R, et al. Fatal multiorgan failure due to yellow fever vaccine-associated viscerotropic disease. Vaccine 2007;25:8480-8485
[13] Doblas A, Domingo C, Bae HG, Bohórquez, de Ory F, Niedrig M et al. Yellow fever vaccine-associated viscerotropic disease and death in Spain. J Clin Virol 2006; 36:156-158.
[14] Gerasimon G, & Lowry K. Rare case of fatal yellow fever vaccine-associated viscerotropic disease. South Med J 2005;98(6):653-6.
[15] Muñoz J, Vilella A, Domingo C, Nicolas JM, de Ory F, Corachan M, et al. Yellow fever-associated viscerotropic disease in Barcelona, Spain. J Travel med 2008;15(3):202-5.
[16] Pulendran B, Miller J, Querec TD, Akondy R, Moseley N, Laur O, et al. Case of yellow fever vaccine-associated viscerotropic disease with prolonged

viremia, robust adaptive immune responses, and polymorphisms in CCR5 and RANTES Genes. J Infect Dis 2008,198(4):5000-7.
[17] Whittembury A, Ramirex G, Hernández H, Ropero AM, Waterman S, Ticona M, et al. Viscerotropic disease following yellow fever vaccination in Peru. Vaccine 2009;27:5974-5981.
[18] Adhiyaman V, Oke A, Cefai C. Effects of yellow fever vaccination. Lancet 2001;358(9296):1907-1908.
[19] Werfel U, Poop W. Effects of yellow fever vaccination. Lancet 2001;358(9296):1909
[20] Centers for Disease Control and Prevention (CDC). Adverse events associated with 17D-derived ywllow fever vaccination—United States, 2001-2002. MMWR Morb Mortal Wkly Rep 2002;51(44):989-93.
[21] Cetron MS, Marfin AA, Julian KG, Gubler DJ, Sharp DJ, Barwick RS, et al. Yellow fever vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2002. MMWR Recomm Rep 2002;51(RR-17):1-11.
[22] Chan RC, Penney DJ, Little D, Carter IW, Roberts JA, Rawlinson WD. Hepatitis and death following vaccination with 17D-204 yellow fever vaccine. Lancet 2001;358(9276):121-2.
[23] Kitchener S. Viscerotropic and neurotropic disease following vaccination with the 17D yellow fever vaccine, ARILVAX. Vaccine 2004; 22(17-18):2103-5.
[24] Martin M, Tsai TF, Cropp B, Chang GJ, Holmes DA, Tseng J, et al. Fever and multisystem organ failure associated with 17D-204 yellow fever vaccination: a report of four cases. Lancet 2001;358(9276): 98-104.
[25] Vasconcelos PF, Luna EL, Galler R, Silva LJ, Coimbra TL, Barros VL, et al. Serious adverse events associated with yellow fever 17DD vaccine in Brazil: a report of two cases. Lancet 2001, 358(9276):91-7.
[26] Troillet N, Laurencet F. Effects of yellow fever vaccination. Lancet 2001;358(9296):1908-9.
[27] Kennedy CC, Mullon J. Yellow fever vaccine associated viscerotropic disease in a young woman: a rare complication of a common vaccine. Crit Care Med 2007; 35(12).
[28] Agencia Española del Medicamentos y Productos Sanitarios edit by Eurosurveillance editorial team. A death associated with yellow fever vaccination reported in Spain. Eurosurveillance 2004;8(45):1-3.
[29] Douce RW, Freire D, Tello B, Vásquez GA. Case report: A case of yellow fever vaccine-associated viscerotropic disease in Ecuador. Am J Trop Med Hyg 2010;82(4):740-742.
[30] Vasconcelos PFC, Bryant JE, da Rosa TP, Tesh RB, Rodrigues SG, Barrett AD. Genetic divergence and dispersal of yellow fever virus, Brazil. Emerg Infect Dis 2004;10(9):1578-84.
[31] Struchiner CJ, Luz PM, Dourado I, Sato HK, Aguiar SG, Ribeiro JG, et al. Risk of fatal adverse events associated with 17DD yellow fever vaccine. Epidemiol Infect 2004;132(5):939-46.
[32] Breugelmans G, Lewis R, Perea W, Niedrig M, Gessber B, Yactayo S, et al. Yellow fever adverse events following immunization in Africa: development of

a standardized database for analysis and presentation of safety data. Version prior to print.
[33] de Menezes Martins R, de S. Maia M, dos Santos EM, de S. Cruz RL, dos Santos PR, Carvalho SM, et al. Yellow fever vaccine post-marketing surveillance in Brazil. Procedia Vaccinol 2010;2(2):178-83.
[34] PAHO/WHO statement. Investigation of serious adverse events in Peru following receipt of yellow fever vaccine produced by Bio-Manguinhos, Brazil. 21 March 2008
[35] Belmusto-Worn VE, Sanchez JL, McCarthy K, Nichols R, Bautista CT, Magill AJ, et al. Randomized, double-blind, phase III, pivotal field trial of the comparative immunogenicity, safety, and tolerability of two yellow fever 17D vaccines (Arilvax and YF-VAX) in healthy infants and children in Peru. Am J Trop Med Hyg 2005;72(2):189-97.
[36] Fitzner J, Coulibably D, Kouadio DE, Yavo JC, Loukou YG, Koudou PO, et al. Safety of the yellow fever vaccine during the September 2001 mass vaccination campaign in Abidjan, Ivory Coast. Vaccine 2004;23(2):156-62.
[37] Roukens AH, Soonawala D, Joosten SA, de Visser AW, Jiang X, Dirksen K, et al. Elderly subjects have a delayed antibody response and prolonged viraemia following yellow fever vaccination: A prospective controlled cohort study. PLoS One 2011,6(12):e27753.