



Review

Active and passive surveillance of yellow fever vaccine 17D or 17DD-associated serious adverse events: Systematic review

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ARTICLE INFO

Article history:

Received 3 February 2011

Received in revised form 12 April 2011

Accepted 18 April 2011

Available online 5 May 2011

Keywords:

Yellow fever

Yellow fever 17D and 17DD vaccine

Serious adverse effects

Active surveillance

Systematic review

Risk of bias

ABSTRACT

Purpose: To identify the rate of serious adverse events attributable to yellow fever vaccination with 17D and 17DD strains reported in active and passive surveillance data.

Methods: We conducted a systematic review of published literature on adverse events associated with yellow fever. We searched 9 electronic databases for peer reviewed and grey literature in all languages. There were no restrictions on date of publication. Reference lists of key studies were also reviewed to identify additional studies.

Principal results: We identified 66 relevant studies: 24 used active, 17 a combination of passive and active (15 of which were pharmacovigilance databases), and 25 passive surveillance.

Active surveillance: A total of 2,660,929 patients in general populations were followed for adverse events after vaccination, heavily weighted (97.7%) by one large Brazilian study. There were no observed cases of viscerotropic or neurotropic disease, one of anaphylaxis and 26 cases of urticaria (hypersensitivity). We also identified four studies of infants and children ($n = 2199$), four studies of women ($n = 1334$), and one study of 174 HIV+, and no serious adverse events were observed.

Pharmacovigilance databases: 10 of the 15 databases contributed data to this review, with 107,621,154 patients, heavily weighted (94%) by the Brazilian database. The estimates for Australia were low at 0/210,656 for “severe neurological disease” and 1/210,656 for YEL-AVD, and also low for Brazil with 9 hypersensitivity events, 0.23 anaphylactic shock events, 0.84 neurologic syndrome events and 0.19 viscerotropic events cases/million doses. The five analyses of partly overlapping periods for the US VAERS database provided an estimate of 6.6 YEL-AVD and YEL-AND cases per million, and estimates between 11.1 and 15.6 of overall “serious adverse events” per million. The estimates for the UK were higher at 34 “serious adverse events” and also for Switzerland with 14.6 “neurologic events” and 40 “serious events not neurological”/million doses.

Passive surveillance: Six studies of campaigns in general populations included 94,500,528 individuals, very heavily weighted (99%) by the Brazilian data, and providing an estimate of 0.51 serious AEFIs/million doses. Five retrospective reviews of hospital or clinic records included 60,698 individuals, and no serious AEFIs were proven. The data are heavily weighted (96%) by the data from the Hospital for Tropical Diseases, London. Two studies included 35,723 children, four studies included 138 pregnant women, six studies included 191 HIV+ patients, and there was one review of patients who were HIV+, and no serious AEFIs were proven.

Major conclusions: The databases in each country used different definitions, protocols, surveillance mechanisms for the initial identification and reporting of cases, and strategies for the clinical and laboratory follow up of cases. The pharmacovigilance databases provide three sets of estimates: a low estimate from the Brazilian and Australian data, a medium estimate from the US VAERS data, and a higher estimate from the UK and Swiss data. The estimates from the active surveillance data are lower (and strongly influenced

Abbreviations: AEFI, adverse event following immunization; PCR, polymerase chain reaction; YEL-AND, yellow-fever associated neurologic disease; YEL-AVD, yellow-fever associated viscerotropic disease; YFV, yellow fever vaccine.

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by the Brazilian data) and the estimates from the passive surveillance studies are also lower (strongly influenced by the London Hospital for Tropical Diseases data from the early 1950s). Sophisticated pathology, histopathology and tests such as PCR amplicon sequencing are needed to prove that serious adverse events were actually caused by the yellow fever vaccine, and the availability of such diagnostic capability is strongly biased towards recent reports from developed countries. Despite these variations in the estimation of serious harm, overall the 17D and 17DD yellow fever vaccine has proven to be a very safe vaccine and is highly effective against an illness with high potential mortality rates.

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1. Introduction

Yellow fever (YF) is a mosquito-borne viral disease with reported fatality rates ranging from 20% to 80% due to two principal syndromes: YEL-AND (yellow-fever associated neurologic disease, which includes encephalitis, myelitis or myelo-encephalitis [ADEM]), and YEL-AVD (yellow-fever associated viscerotropic disease, which usually involves multi-organ failure including liver, renal and circulatory failure) [1]. Yellow fever is present in both the rural and urban tropical areas of 45 endemic countries in Africa and Latin America, with a potential combined population of over 900 million individuals.

Serious adverse events attributable to vaccination include YEL-AND, YEL-AVD and anaphylaxis. Overall, yellow fever vaccine has very low reported rates of adverse events as evidenced by the more than 600 million doses have been successfully distributed since 1939, but there has been a series of reports of serious adverse events after yellow fever vaccine [2–13]. There is thus the need to continue to protect by vaccination hundreds of millions of individuals in endemic countries, but determine the rates of serious adverse events, and identify risk factors for serious adverse events for certain populations, such as HIV positive individuals.

The Brighton Collaboration envisaged developing guidelines for the standardized collection, analysis and presentation of vaccine safety data [14] which would require 50–100 guidelines for standardized case definitions of AEFIs [15] and to date 24 guidelines have been developed [16]. The Brighton Collaboration [17] specified for surveillance systems 45 detailed criteria for a “desirable standard for collection of vaccine safety data,” and these 2009 Guideline proposals harmonise with the ICH and CIOMS guidelines [18,19].

Although the guidelines specify the optimum amount and quality of data to be collected to assess definitively if an adverse event or a serious adverse event can be attributed to yellow fever vaccine, organizations may not have enough resources or trained staff to implement the guidelines in full, and the quality of data from both active and passive surveillance systems needs to be assessed. Active surveillance for AEFIs requires regular assessment in person of all vaccinated individuals by specifically trained assessors. In the

case of yellow fever vaccine the differential diagnosis for the symptoms of possible serious neurologic AEFIs includes a wide range of pathogens that can cause encephalitis/meningitis-like symptoms, and for serious viscerotropic syndrome includes a wide range of pathogens that can cause liver and multi-system failure. Specific laboratory investigations are required to rule in yellow fever vaccine and rule out other pathogens.

We defined active surveillance as occurring when the study design and execution achieved or had the likelihood of a high success rate in identifying both every person who received yellow fever vaccine and following them through the first 30 days after vaccination to assess serious adverse reactions such as AND or AVD by collecting all the data required to make a definitive judgment. An example of active surveillance is Belmusto-Worn et al. [20]:

All AES were recorded in the case report forms, including severity, the investigator's assessment of causality (relationship to study vaccine), start date and end date, and whether treatment was required. Children failing to attend scheduled visits were visited at home. Parents/guardians were instructed to return to the clinic if the child developed a fever (oral temperature $\geq 38\text{C}/100.4\text{F}$) or if they were in any way concerned with the health of their child during the follow up period (days 1–31). Subjects who developed a generalized febrile illness within the first 10 days post-vaccination were carefully evaluated. The study's on-site investigator determined if there was a plausible explanation for the illness, such as a respiratory infection. If there was no plausible explanation, a blood sample was taken to help determine the nature of illness (by liver function tests and viremia) [20].

The preface to the Brighton Guidelines [17] notes the limitations that can occur with passive surveillance for AEFIs: underreporting, variable and often incomplete reports, the high frequency of incomplete follow-up of outcome information, limited or no access to hospital or laboratory records, lack of a reliable denominator, and inability to determine the temporal relationship of the vaccine to an AEFI. The Guidelines note, however, that passive surveillance systems can provide advantages: large numbers of reports over time, and the ability to observe trends in cases and clusters which can

lead to improved epidemiological monitoring and investigation. The authors of the Brighton guidelines for anaphylaxis identified two main barriers to implementation of their detailed Guideline: health care providers are unlikely to spontaneously report enough symptoms and signs to allow application of the Brighton Guidelines, and reporters are likely to be inconsistent in the use of terms. To improve the data collected about anaphylaxis by passive surveillance systems they provide an abbreviated checklist for primary care providers, and such abbreviated checklists may be helpful in improving data collection in surveillance systems, reserving the full guidelines for RCTs or studies with adequate resources to implement them.

We defined passive surveillance as occurring when the data collection process gathered information from persons and data about serious adverse effects in a passive manner such that the total number of individuals and the data used to make definitive judgments about the individuals is known to be incomplete or runs a risk of being incomplete. An example of passive surveillance is Oyelami et al. [21]:

“An unusual outbreak of post-vaccination reactions to 17D yellow fever vaccine in Shaki, Nigeria, May 1987.” Passive surveillance consisted of studying the 25 patients who presented at the Baptist Hospital, Shaki, with: “... rapidly progressing swelling of the left arm, fever and associated constitutional symptoms...” [21] [i.e. no attempt to track down each vaccinee and assess symptoms]

An example of a combination of active and passive surveillance is Nasidi et al. [22]:

Follow-up of the subjects was carried on both passively, when the pregnant women called at the hospital for routine medical visits or for tetanus toxoid vaccinations, or actively, when they were visited at their homes by the social workers or hospital staff. Information about a pregnant woman or about mother and child was obtained regularly at intervals of about 2–8 weeks. Physical examination of both mother and child or pregnant women was done regularly. Newborn children were monitored using established indices for child growth and development [22].

Our research objective was to assess and compare the rates of serious adverse events following yellow fever vaccination as reported through active and passive surveillance methods, and assess possible reasons for any differences in estimates.

2. Methods

We searched these electronic databases: the Cochrane Library, including the 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 1980 to present), BIOSIS Previews (ISI 1980 to present), Global Health (OVID 1910 to present), CAB Abstracts (OVID 1910 to present), and the Lilacs Database of Latin American and Caribbean literature to identify studies appropriate for inclusion in this review. A list of search terms is available by contacting the authors. The searches included all languages. No date limits were applied. Web of Science and PubMed's Related Articles feature were used to identify additional articles that cite relevant studies retrieved through database searching. Reference lists of included papers were scanned to identify additional studies of relevance.

All abstracts were independently read by two reviewers and included if they reported data on or risk factors associated with serious yellow fever vaccination adverse events. If relevance could

not be judged on the basis of the title or abstract, the full text article was read independently by two reviewers. Disagreements at any stage were resolved by consensus or referral to a third reviewer.

Serious adverse events included YEL-AND, YEL-AVD, anaphylaxis/hypersensitivity and other life threatening events. Life threatening events were defined as medical conditions which could in theory result in death or severe disability affecting a person's autonomy, even if the affected individuals do not suffer any of these outcomes during the course of their illness [23].

We computed the 95% confidence limits for serious adverse event rates for studies where active surveillance methods were present for an appropriate duration to ensure that all serious AEFIs were detected, a reasonable estimate of the denominator was presented, and only where we could group studies to achieve more than one million vaccinees. We did not compute rates for smaller numbers as when we observed the high apparent upper limits and the imprecision of the estimates concerns could be erroneously ascribed to the safety of the vaccine rather than appropriately ascribed to the small size of the studies. For example, if a study with 200 subjects identified no serious AEFIs, the upper limit for the serious AEFI 95% confidence interval could be as high as one expected event per 55 vaccinations, and the overall literature suggests this is completely unrealistic. For zero rate estimates the lower limit of the 95% confidence interval is negative, which does not make sense, and instead is reported as zero.

For RCTs we followed the Cochrane Collaboration *Handbook* and RevMan 5.1 software in assessing six sources of bias: randomization, concealment of allocation, blinding, incomplete data, selective reporting, and other sources of bias.

3. Results

3.1. Literature search

We identified 2415 abstracts, of which 472 were selected for full text review. Of the 201 studies included in the review 24 used active surveillance (of which 10 were RCTs), 17 used a combination of active and passive surveillance (of which 15 were pharmacovigilance databases) [20,22,24–47] and 25 used passive surveillance (Fig. 1).

3.2. Active surveillance: general populations

We identified 17 studies of general populations [25,27–32,34–36,38,40–42,46,24,48] but only 14 [25,27,29–32,34–36,40–42,46,48] contributed to the analysis as the follow up was too brief in three to detect all serious AEFIs. Seven of these 14 studies were RCTs [25,32,34–36,40,42]. Two of the RCTs were of military personnel [36,42] and both were at moderate risk of bias: neither described a strong method of randomisation, concealment or blinding. Five of the RCTs were of populations in the community [25,32,34,35,40] and two of these were at low risk of bias [25,32] and three at moderate risk [34,35,40]. Only one RCT described a strong method of randomisation [25]; three RCTs were described as double-blind with no further description [25,32,35], and three provided reporting for nearly all participants [25,32,40].

A total of 2,660,929 patients were followed for adverse events after vaccination, heavily weighted (97.7%) by one large study [30]. There were no observed cases of viscerotropic or neurotropic disease, one of anaphylaxis and 26 cases of urticaria (hypersensitivity). Fitchner's active surveillance techniques [30] were comprehensive: personnel were trained on AEFI diagnosis and were asked to call an ambulance in the case of an acute AEFI; supervisors then completed AEFI forms, which were reviewed by their own supervisors;

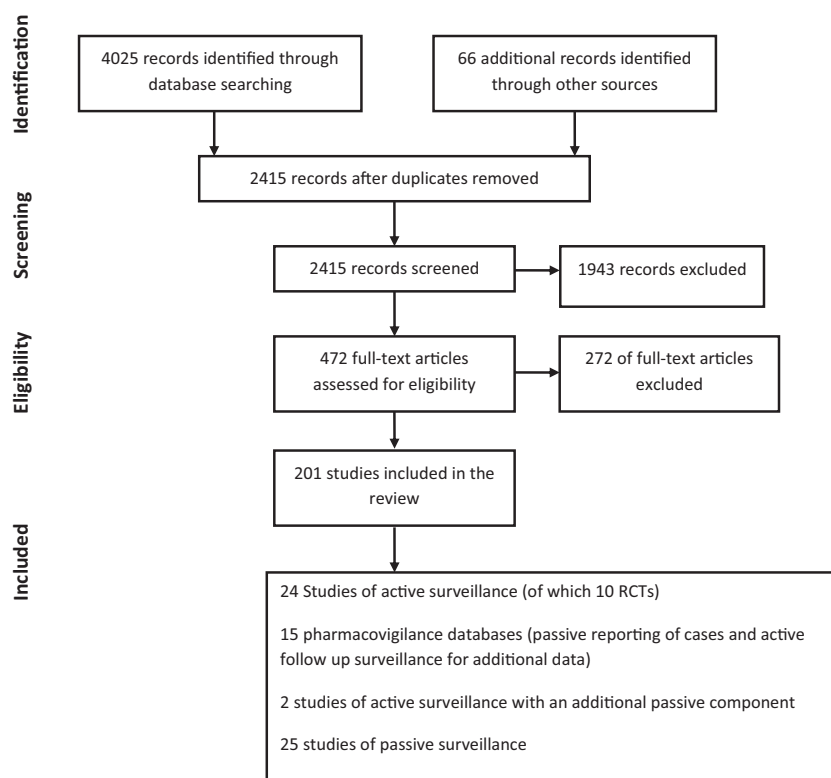


Fig. 1. PRISMA flow sheet of assessment of cases.

the 57 major health facilities, including all hospitals in Abidjan, were informed about surveillance methods, case definitions of suspected yellow fever and AEFIs; physicians telephoned the facilities daily during the campaign and until four weeks after the campaign to ascertain if possible cases had presented; physicians ascertained cases by visits to patients, reviewed the patient's history, collected blood samples and additional samples to exclude coincidental illnesses, and completed assessment forms; and a pharmacovigilance expert committee reviewed this data on the AEFIs and decided further case investigations.

Based on this group of studies which used active surveillance, dominated by Fitzner's large study, we suggest the 95% confidence interval for anaphylaxis is 0.009–2.1 events per million vaccinations, or equivalently, at most one anaphylactic event is expected in every 480,000–105 million vaccinations. For hypersensitivity, the 95% confidence interval is between 6.4 and 14.3 expected events per million vaccinations, or equivalently, we expect one case of hypersensitivity in every 70,000–150,000 vaccinations. For viscerotropic and neurotropic disease, the expected 95% confidence interval is for a rate between 0 and 1.39 events per million doses, or equivalently, at most one event per 720,000 (Table 2).

Active surveillance: Infants and children, pregnant females, HIV+ individuals, and individuals with rheumatological diseases (Table 3).

We identified four studies of infants and children [20,33,37,44] all of which were RCTs. Two RCTs are at low [20,37] and two at moderate [33,44] risk of bias. None described the method of randomisation other than to say that the children "were randomised," i.e. they did not describe a strong method of randomisation. Two described concealment of the allocation from the researchers and blinded participants [20,44]. Not surprisingly in studies of vaccinating children, two of the four studies experienced attrition of participants.

A total of 2199 children were vaccinated and no serious adverse events were recorded. A small amount of data is available and the

serious adverse events rate is thus associated with a wide confidence interval. The observed serious adverse events rate was zero, suggesting that the best estimate of the serious risk from adverse events is zero. However, as there are very little data, that number could be as high as 1.67 expected serious adverse events/1000 vaccinations. The primary conclusion is that more data is needed specifically on infants and children to accurately assess the true risk of serious adverse events in this population.

We identified four studies of pregnant women [22,26,39,45], which included 1334 cases. Rates of adverse events above those routinely expected in pregnancy were not found. Similar to the situation with the infants and children, we have insufficient data to obtain a reasonably precise estimate of the serious adverse events rate among these women. It was observed that there was no increased risk of serious pre- or post-natal adverse outcomes among these 1334 women. Statistically speaking, the rate of serious adverse events rate could be as high as 2.77/1000 vaccinations, at the 95% confidence level but it should be made clear that it could also be as low as zero events. More data are required to be certain of the actual serious adverse event rate.

We identified one study [47] of 174 HIV+ individuals who had received 17D or 17DD, and no serious adverse events were observed. Veit et al. [49] reviewed the literature on serious adverse events in HIV+ individuals post YFV and concluded the risk for serious adverse events is unknown.

3.3. Combined active and passive surveillance: pharmacovigilance databases

Pharmacovigilance databases combine a passive surveillance system (awaiting reports) and then an active system of following up reports for more details. We identified 15 pharmacovigilance databases [8,12,35,50–61] of which 10 contributed data to this review [8,12,35,55–61]. There are five analyses of partly overlapping periods for the US VAERS database [8,12,55,58,61] for

Table 1

Study surveillance methods and adverse events.

Author, country, vaccine, participants	Active surveillance method	Serious yellow fever vaccine-associated adverse events
<i>Military personnel or prisoners</i>		
Dick [28] 17D; Uganda 1946; 103 male Africans Central Prison, Luzira vaccinated by scarification 1/10 recommended dosage; 107 by subcutaneous injection, diluted 1/10	Daily sick parade [did not contribute data to this review as dosages 1/10 of recommended dose]	0 off-duty or hospitalizations
Dick and Horgan [27] female patients mental hospital Uganda; 17D; 25 by scarification combined YFV and smallpox; 25 subcutaneously YFV and scarification with smallpox	Daily medical supervision by physician; examined by authors 2, 8 and 28 days after vaccination	0
Edwan [29] 17D; Jordanian peacekeepers in Eritrea, 2002; also hepatitis B, typhoid, meningitis, tetanus 1 month later (n = 963)	Instructed to report to health care providers any adverse reactions; form about expected complications filled by vaccination team	0
Hahn [31] 17D; “volunteers” in Nigerian leprosarium 1969; 20 17D; 20 also smallpox	Surveillance for 6 months; temperatures twice daily; all intercurrent illnesses observed for several weeks	0
Moss-Blundell et al. [36] RCT; 17D; UK; Sandhurst Cadets at received smallpox, oral polio, typhoid/paratyphoid/tetanus or typhoid vaccines 3 and 7 weeks before YFV (n = 668)	Vaccinees questioned about vaccination reactions 2 and 11 weeks; 90 kept a diary for 10 days after vaccination	0
Roche et al. [42] RCT; French naval recruits; 17D (n = 297)	Vaccinees remained in Unit 1 month, followed by physicians of the recruits’ Unit	0
Tauraso et al. [46] U.S Midshipmen, 1970; 17D; also smallpox vaccine (n = 526)	Interview and physical exam to assess response to smallpox vaccine	0
<i>Community residents</i>		
Ambrosch et al. [24] Austria; medical students; 17D plus Typhim Vi; (n = 209)	Self-surveillance questionnaires for recording local reactions days 0–7 [did not contribute data to this review as only monitored to day 7]	0 (only monitored until day 7)
Camacho et al. [25] RCT; Brazil; 17DD (n = 538); 17D (n = 269); placebo (n = 271)	Past and current health conditions; all signs, symptoms, medical procedures within 30 days; diary cards; liver enzymes before vaccination, also between days 4 and 20, and 30 days after	0
Fitzner et al. [30] Ivory Coast; 2001; 17D; age > 9 months; 17D (n = 2.6 million)	Personnel trained on AEFI diagnosis and to call ambulance for acute AEFI; supervisors completed AEFI forms, reviewed by their supervisors; 57 major health facilities including all hospitals in Abidjan informed about surveillance, case definitions of suspected yellow fever and AEFI; physicians called facilities daily during campaign and until four weeks after campaign for cases; physicians ascertained cases by visit to patients, completion of forms, reviewed patient history, collected blood sample and additional samples to exclude coincidental illnesses; pharmacovigilance expert committee reviewed AEFIs, decided further case investigations	26 urticaria, 1 anaphylactic shock
Lang et al. [32] RCT; UK; 17D (n = 211)	Self-monitoring form for systemic events within 28 days; liver function tests before and 28 days after vaccination; follow up 10–14 days and 1 month	0
Monath [34] RCT; US; 17D (n = 1440)	Telephone interview day 5, in clinic days 11 and 31; diary days 1 through 10; scripted questions to prompt reporting systemic reactions	0
Monath et al. [35] RCT; UK; 17D “Most... did not receive another vaccine.” (n = 3092)	Diary checked by a scripted interview days 14 and 35	0
Panthier and Husson [38] Institut Pasteur, Paris; 17D; 1953–1957 (n = 18,006)	Patients with allergies tested with intradermal YFV injection; only assessed during clinic so only severe adverse reactions on first day could have been observed [did not contribute data to this review as patients only monitored for 20 min]	1 allergic reaction with asthma (patients only monitored for 20 min)
Pfister et al. [40] RCT; healthy adults 18–60 years old; (n = 304)	Diary card days 1–14; follow-up visit day 29	0
Pivetaud et al. [41] Bordeaux; 17D; age > 1 year (n = 370)	Contacted by phone or questioned during a second vaccination.	0
Smith et al. [43] 17D; Brazil; Paraguay; mostly workers on rural fazendas (estates); (n = 52,052)	“... arrangements were made for the sanitary inspector and technical assistant to live on the fazendas and interview each vaccinated person daily, taking his temperature and carefully noting any symptoms which occurred. One of the doctors made daily visits to each fazenda to examine any person who complained of symptoms.... the failure of any vaccinated person to report for work could be promptly noted and investigated. The inspector had instructions to telephone immediately to the doctor in charge should any severe or unusual reactions be observed.”	0
<i>Infants and children</i>		
Belmusto-Worn et al. [20] RCT; Peru; 2002; 17D (n = 1107)	Case reports (severity and causality assessment); children not attending scheduled visits visited at home; parents/guardians instructed to return to clinic if child fever $\geq 38^{\circ}\text{C}$ or any concerns days 1 to 31; children with fever in first 10 days evaluated; study on-site investigator determined if plausible explanation, blood sample for liver function tests and viremia	0

Table 1 (Continued)

Author, country, vaccine, participants	Active surveillance method	Serious yellow fever vaccine-associated adverse events
Lhuillier et al. [33] RCT; Ivory Coast; 17D and measles vaccine; infants 6–9 months; (n = 219)	Questioned mother; analysis of reasons for visiting dispensaries	0
Osei-Kwasi et al. [37] RCT; 17 D; Ghana; also received BCG, OPV, DPT; (n = 420)	Mothers instructed to come to clinic if child unwell; clinic visit day 10 (temperature measured, information on adverse reactions with questionnaire); those not attending visited at home	0
Soula et al. [44] RCT; Mali; 17D and/or measles vaccine; children 6–24 months; 1988–9; (n = 453)	Temperatures days 2, 7, 14; enquiry for general reactions (rash, cough, conjunctivitis, gastro-intestinal troubles, convulsions, general malaise and any other signs discovered by the investigator)	0 (surveillance only up to 14 days)
<i>Pregnant females</i>		
Cavalcanti et al. [26] Campinas Region Brazil; 17DD; pregnant women who inadvertently received YFV (n = 312)	304 babies exposed in utero followed up at birth and 1 month to 1 year; compared to 10,691 births in the region 1997–1999 for structural defects in exposed babies.	No differences in 7 types of major malformations except Down's Syndrome (3 cases in babies exposed in utero to YFV)
Nasidi et al. [22] Nigeria; 17D; pregnant females aged 15–50; 1986–7 (n = 101)	Routine medical visits; home visits; regular physical examinations; newborns monitored for growth and development	0; no physical or psychological abnormality
Papaiordanou et al. [39] Campinas Region, Brazil; 17DD; pregnant women inadvertently vaccinated during campaign; 91% <13 weeks pregnant at vaccination (n = 488)	Prospective cohort evaluated adverse effects, seroconversion, perinatal results and teratogenicity (98% mothers had YF antibodies)	0
Suzano et al. [45] Campinas Region, Brazil; 17DD; 480 pregnant women vaccinated inadvertently at average 5.7 weeks gestation; (441 followed up)	3 antenatal visits; for women from Campinas placenta and umbilical cord PCR, neonatal serology (IgM by MAC-ELISA, IgG by PRNT; transfontanel ultrasound, brainstem-evoked response audiometry; fundoscopy, clinical dysmorphic and neurological exam, and visits at 3, 6 and 12 months for clinical and serological evaluation)	98.2% women + YF IgM 6 weeks after vaccination. No IgM antibodies at birth in any infant, 0 of 15 RT-PCR samples from cord blood or placenta positive; 304 evaluated by geneticist: all rates similar to general population
<i>HIV + patients</i>		
Veit et al. [47] Swiss HIV Cohort Study; 4 of 7 centres participated; individuals reporting journey to tropical destination 1996–2005; standardised criteria on structured forms at enrolment and at 6 monthly follow-up; plasma samples at each visit (n = 102)	Asked during about travel, 17D and immunosuppressive medication during consultation, by phone, questionnaires or chart reviews; vaccination card checked for other live vaccines; charts for deceased patients checked for correlation of death to 17DV receipt or AE; Swiss vaccination surveillance system queried for SAEs after 17D	9181 participants in SHCS (2648 had traveled to a tropical country, 696 evaluated for 17D); report focused on 102 who received 17D after HIV diagnosis; no AEFIs

RCT = randomized controlled trial; AEFI = adverse event following immunization; YFV = yellow fever vaccine; 17D = 17D strain of yellow fever vaccine; 17DD = 17DD strain of yellow fever vaccine; MAC-ELISA = M antibody-capture enzyme-linked immunosorbent; PRNT = plaque reduction neutralization test.

1990–2006, with about 3,303,000 vaccinations; one of the Brazilian system with 101,564,083 [59]; two of the Australian database with 210,656 [56,57]; one of ARILVAX in the UK with 1,043,415 [35]; and a Swiss database with 1,500,000 [60].

3.4. US VAERS system

Martin et al. [58] reviewed reports 1990–1998 of “death, hospitalization, or disability, a life-threatening illness, or illness requiring an emergency room or doctor visit.” A systemic adverse event was defined as “a multi-systemic (excluding anaphylaxis) or neurologic

Table 2

Serious adverse events in studies of patients who received 17D or 17DD yellow fever vaccine: general populations, active surveillance.

Section	Author (year)	Vaccinations	Hyper-sensitivity	Neurotropic disease	Viscero tropic disease	Anaphylaxis
Military	Moss-Blundel et al. (1981) [36]	668	0	0	0	0
	Edwan (2004) [29]	963	0	0	0	0
	Roche et al. (1986) [42]	297	0	0	0	0
	Tauraso et al. (1972) [46]	526	0	0	0	0
Hospitals/prisons	Dick and Horgan (1952) [27]	50	0	0	0	0
	Hahn (1951) [31]	40	0	0	0	0
Community RCTs	Camacho et al. (2005) [25]	807	0	0	0	0
	Lang et al. (1999) [32]	211	0	0	0	0
	Monath et al. (2005) [34]	1440	0	0	0	0
	Monath et al. (2005) [35]	3092	0	0	0	0
	Pfister et al. (2005) [40]	304	0	0	0	0
Community vaccination campaigns	Fitzner et al. (2004) [30]	2,600,000	26	0	0	1
	Smith et al. (1938) [43]	52,052	0	0	0	0
	Pivetaud et al. (1986) [41]	479	0	0	0	0
TOTAL	2,660,929	26	0	0	1	
95% Confidence interval for serious AEFI rate per million vaccinations			6.4–14.3	0–1.39	0–1.39	0.009–2.1
One expected event per			70,000–150,000	720,000 at most	720,000 at most	480,000–105 million

AEFI = adverse event following immunization; 17D = 17D strain of yellow fever vaccine; 17DD = 17DD strain of yellow fever vaccine.

Table 3
Serious adverse events in studies of patients who received 17D or 17DD yellow fever vaccine: infants and children, pregnant females, and HIV+ patients, active surveillance.

Section	Author (year)	Vaccinations	Hyper-sensitivity	Neurotropic disease	Viscero tropic disease	Anaphy laxis
Infants and Children	Belmusto-Worn et al. (2005) [20]	1107	0	0	0	0
	Lhuillier et al. (1989) [33]	410	0	0	0	0
	Osei-Kwasi et al. (2001) [37]	420	0	0	0	0
	Soula (1991) [44]	453	0	0	0	0
Pregnant females	Cavalcanti et al. (2007) [26]	312	0	0	0	0
	Nasidi et al. (1993) [22]	101	0	0	0	0
	Papaioordanou et al. (2001) [39]	488	0	0	0	0
	Suzano et al. (2006) [45]	441	0	0	0	0
HIV+	Veit et al. (2009) [47]	102	0	0	0	0

Lhuillier et al. [33] and Nasidi et al. [22] used active surveillance with an additional passive component; 17D = 17D strain of yellow fever vaccine; 17DD = 17DD strain of yellow fever vaccine.

reaction.” “Other adverse events” were defined as “uncomplicated neurologic or systemic, hypersensitivity or local reaction” and were not included. Events in children <15 years or military personnel were excluded as “no adequate estimates of the number of persons who received yellow fever vaccine in these groups were available.” Three physicians independently reviewed the reports. Martin identified 16 systemic adverse events in which the individual had received only yellow fever vaccine, and 19 in which other vaccines had been administered. There were also 36 “other adverse events” (defined as uncomplicated neurologic/systemic, hypersensitivity or local reactions). The authors extrapolated the data on vaccine purchases for 1995–9 and estimated that civilian providers purchased 1,443,686 doses of yellow fever vaccine 1990–1998. We, therefore, estimate a rate of 11.1 “systemic adverse events” per million doses.

Khromava et al. [55] reviewed reports for an overlapping period (1990–2002). Khromava reported that serious adverse events are followed up by telephone to obtain additional information about the events and the patient’s medical history, and the serious events are presented to the Yellow Fever Vaccine Safety Working Group for discussion of a possible causal relationship to vaccination. In addition, for events similar to YEL-AVD or YEL-AND, serum and/or CSF samples are requested for YF IgM or IgG testing at the CDC. Khromava did not report the detailed results of this arbitration procedure. Khromava identified 7 YEL-AVD and 8 YEL-AND civilian cases and one YEL-AVD and two YEL-AND military cases. There were 32 other serious events where yellow fever was administered with other vaccines. A total of 722 yellow fever vaccine-associated events were reported, of which 465 were civilian (430 non-serious) and 257 military (245 non-serious). In 190 (26%) of the reports yellow fever vaccine was administered alone, in 390 (50%) with Typhoid, Hepatitis or other vaccines, and Khromava does not report vaccines for the remaining 24%. Khromava combined the reports for serious adverse events for yellow fever vaccine administered alone and with other vaccines and based her estimated rates on these combined numbers. Khromava estimated that civilian providers purchased an estimated 2.2 million doses and the military 7.4 million doses 1990–2002. For the civilian cases we compute a rate of 6.6. YEL-AVD and YEL-AND cases per million. Because the military may stockpile doses and not use them, we did not compute a rate for the military.

Lindsey et al. [8] reviewed adverse events 2000–2006 and chose a 60 day interval after YF administration in which to accept the report of an adverse event, unlike the usual interval of 30 days after yellow fever vaccination. Table 1 of Lindsey’s article reports 190 events which followed the administration of 17D alone: 24 adverse events were noted (including one death, seven life-threatening illnesses, 21 hospitalisations, and one prolongation of a hospitalisation).

Table 1 also reports 470 adverse events in which 17D was given in combination with other vaccines. There were 48 serious adverse

events (including 3 deaths, 14 life-threatening illnesses, 37 hospitalisations, 4 prolongations of a hospitalisation, and 7 cases of permanent disability). Lindsey’s Tables 2 and 4 combine the 660 adverse events for the individuals who received 17D alone and 17D with other vaccines, and reported 28 cases of anaphylaxis, 12 YEL-AND, and 6 YEL-AVD. Because Table 1 reports 24 serious adverse events, and these 18 YEL-AND and YEL-AND cases must by definition be included in this group, we decided to accept 24 as the total of serious adverse events. Lindsey estimated the total number of doses of YF vaccine administered 2000–2006 as 1,534,170. We computed a rate of 15.6 serious adverse events per million.

Souayah et al. [61] reviewed the US VAERS database only for 2004 for cases of Guillain–Barré Syndrome after yellow fever vaccination. Three cases were identified, yellow fever vaccine was given in conjunction with other vaccines, and no case data were provided. Vellozzi et al. [12] was interested in the effect of corticosteroids on the remission of AVD cases and searched the US VAERS database 1996–2004 for cases of YEL-AVD, identified 11 cases and retrospectively searched the medical records of each case for dates of vaccination, onset of adverse events, hospital admission, clinical and laboratory data and administration of steroids.

For older persons Khromava et al. [55] combined the reports for serious AEFIs for YFV administered alone and with other vaccines and based her estimated rates on these combined numbers. Martin et al. [58] reported the rates he computed based on the 19 cases in which YFV alone was administered plus the 16 in which YFV was administered with other vaccines. We have, therefore, not computed rates for older persons because of these limitations.

3.5. Australia, Brazil, UK and Switzerland

Lawrence et al. [57] reviewed reports to the Australian ADRAC database 1993–2002. Systemic adverse events were defined as occurring within two weeks of vaccination. Neurological events were given a broad definition of new onset seizures, encephalitis, myelitis, altered mental status, focal cranial or peripheral neurological deficits, paresthesia, vertigo, ±headache. Multi-systemic events were also broadly defined as myalgia, arthralgia, impaired hepatic function, respiratory distress, nausea, vomiting, impaired renal function, ±fever. Events were classified independently by two authors. The number of doses was extrapolated to 1993–2002 from sales for 1999–2002, and the age distribution of vaccinees was extrapolated for 1992–2002 from a 15% sample of vaccine clinics for 1999–2002. Lawrence identified 42 serious adverse events involving yellow fever vaccine (of which 26 were “systemic” and 9 “serious systemic”). In 15 of the events only yellow fever vaccine was administered, and in 27 yellow fever and other vaccines. Lawrence estimated 210,656 doses of 17D were administered 1993–2002. No cases of “severe neurological disease” were identified and one fatal case of YEL-AVD. Because Lawrence’s definition

was broad we did not compute a rate for “neurological disease” and noted a rate of 0/210,656 for “severe neurological disease” and 1/210,656 for YEL-AVD. The study by Lawrence et al. [56] overlaps his 2004 study, and is not reported here.

Martins et al. [59] reported data from the National Immunizations Program at the Ministry of Health, Brazil 2000–2009. The method is potentially comprehensive: in 1998 a National System for Surveillance of Adverse Events Following Immunization was established, and the WHO Manual for Detection of Serious Adverse Events after YFV and the CDC criteria for classification were adopted. The 30,000 health centres were asked to forward cases to the state level with adjudication at the national level with the capability of identification of yellow fever virus by cell culture, RT-PCR, immunohistochemistry, histopathology, and serology. There is also a network of sentinel hospitals for detecting itohemorrhagic febrile syndromes. A total of 101,564,083 doses of 17DD were administered, and hypersensitivity events were recorded as 9 cases/million doses; anaphylactic shock as 0.23 cases/million doses; yellow fever vaccine-associated neurological disease 0.84/million doses, and 26 viscerotropic cases (19 confirmed, 4 probable, 3 suspect) which yields a rate of 0.19/million doses administered.

Monath et al. [35] assessed age-specific rates of serious AEFIs from reports by physicians of adverse events to the ARILVAX Safety Department, and to the UK Medicines and Healthcare products Regulatory Agency. These were recorded on standard forms from the Council for the International Organization of Medical Sciences (CIOMS), and were independently assessed by three investigators, who then reached consensus using the VAERS definitions. The diagnosis selected was the most serious category reported, and events were excluded if an alternative explanation or diagnosis was available. The definition of a neurologic adverse event included Guillain-Barré syndrome, new onset seizures, encephalitis, myelitis, altered mental status, focal cranial or peripheral neurological deficits, paresthesias, vertigo, or headaches (headaches alone are not sufficient for neurological diagnosis). Multisystemic events included myalgias, arthralgias, rhabdomyolysis, elevated transaminases, respiratory distress, nausea, vomiting, diarrhea, nephropathy, disseminated intravascular coagulation, $\pm$ fever. A total of 1,043,415 doses of ARILVAX 17D (allowing for wastage) were distributed in the UK 1995–1999. The reporting rate denominator for each age group was extrapolated from the UK General Practice Research Database. Using the CIOMS classification [18], 190 adverse events were reported, 36 were classified as serious adverse events and 67 as other adverse events. We computed a rate of 34 “serious adverse events” per million.

Schumacher et al. [60] evaluated reports 1991–2001 of post-vaccination adverse events to the Swiss Government SFOPH organisation. Physicians in Switzerland by law are required to report post-vaccination events, and surveillance involves events within 8 weeks after immunization and data were analysed by the three authors. The results for yellow fever 1991–2001 were: 15 events, with a rate of 5.5 cases/100,000 doses (95%CI: 3.1–9.0). Of the 15 events, 11 were assessed as general systemic reactions and four as neurologic reactions. In terms of severity one was assessed as mild, seven as moderate and seven as serious (not allocated to the previous categories). From Schumacher’s Table 1 we computed the number of yellow fever vaccinations for the period as 1,500,000, and computed a rate of 14.6 cases per million doses for “neurologic events” and 40 per million for “serious events not neurologic.”

The three estimates for the VAERS data base for partly overlapping periods roughly agree: Martin et al. [58] reported 11.1 “systemic adverse events,” Khromava et al. [55] 6.6 YEL-AVD and YEL-AND cases and Lindsey et al. [8] 15.6 “serious adverse events” per million.

There are then two sets of much lower estimates: Lawrence et al. [57] for Australia 0/210,656 for “severe neurological disease” and 1/210,656 for YEL-AVD, and Martins et al. [59] for Brazil: hypersensitivity events were recorded as 9 cases/million doses; anaphylactic shock as 0.23 cases/million doses; yellow fever vaccine-associated neurological disease 0.84/million doses, and 26 viscerotropic cases (19 confirmed, 4 probable, 3 suspect) which yields a rate of 0.19/million doses administered. There are also two sets of much higher estimates: Monath et al. [35] for ARILVAX in the UK reported 34 “serious adverse events” per million, and Schumacher et al. [60] for Switzerland 14.6 cases per million doses for “neurologic events” and 40 per million for “serious events not neurologic.”

It is not possible to choose any set of estimates as more reliable: each system used different definitions and mechanisms for assessing cases, and the differences may also be due to differences in the threshold and mechanisms for the initial reporting of cases.

3.6. Passive surveillance: general populations

For general populations we identified six reports after yellow fever vaccination campaigns [11,13,62–65], and five retrospective studies of clinic or hospital populations [66–70]. The six studies of campaigns in general populations involved 94,500,528 individuals and 48 serious AEFIs, yielding a rate of 0.51 cases/million. The studies are very heavily weighted (99%) by the Brazilian data from Struchiner et al. [11]. Diop Mar et al. [62,63] reported that 67,326 infants were vaccinated with 17D in Senegal and surveillance was limited to children admitted to hospital, and identified 2 cases of encephalitis possibly attributable to 17D, but no confirmatory tests were conducted. Struchiner et al. [11] noted that 93,567,028 doses of 17DD were administered in Brazil 1991–2001 with four fatal events attributed to vaccination, and presented two fatal viscerotropic cases with sequence analysis identification of the RNA of yellow fever vaccine, and Vasconcelos et al. [64] presented two further viscerotropic cases with RNA identification of yellow fever vaccine. Whitembury et al. [13] reported that 42,742 individuals in Peru were vaccinated with Bio-Manguinhos Lot 050VFA121Z in 2007 and five viscerotropic cases were reported of which four were fatal, but 20,432 individuals were vaccinated with a different Bio-Manguinhos lot (050VFA123Z0 and 73,000 with Lot 050VFA121Z) in Venezuela and no serious AEFIs were reported. The WHO [65] reported that 730,000 individuals were vaccinated in the Ivory Coast and 39 cases of “severe reactions” including 8 deaths occurred, with oedema, inflammation and cardiovascular collapse, and reviewers concluded that the illness most closely resembled a Type III hypersensitivity reaction.

The five retrospective reviews of hospital or clinic records involved 60,698 individuals, and no serious AEFIs could be proven. The data are heavily weighted (96%) by Roodyn’s [69] data from the Hospital for Tropical Diseases, London. Kouwenaar [67] identified 3737 individuals who had been vaccinated with 17D at the Institute of Tropical Hygiene, Amsterdam up to 1952: there were data for 1130 individuals, and no serious AEFIs were noted. Roodyn [69] reported that 59,189 persons had been vaccinated with 17D at the Hospital for Tropical Diseases, London, 1951–1954, and stated “it has been extremely rare to hear of any serious effects from the injection. When the infants were brought back after a few days for their primary smallpox vaccination, mothers almost invariably reported that the yellow fever injection had not upset the baby at all.” Roodyn [69] noted 3 cases of meningo-encephalitis after 17D reported by Smith, Haas, and Scott [71–73], but no specific tests for yellow fever vaccine were conducted. Wolga et al. [70] reported on 195 individuals vaccinated with 17D at the Centre Hospitalier Universitaire de Grenoble, and noted no serious AEFIs. Da Mota [66] studied 70 patients with rheumatological diseases in two

Table 4

Preferred techniques for active surveillance of the adverse events of vaccination.

<i>Vaccinees</i>
1. A careful history from each vaccinee concerning previous and current illnesses, medications, travel, other vaccines received in the past, previous yellow fever vaccination. 2. Education of each vaccinee about potential side effects, and when to seek assessment and treatment. 3. Baseline biochemical and infectious diseases measures (a minimal set where relevant would include thick and thin films for malaria parasites, urinalysis, a stool examination for parasites, blood cultures, and CSF if encephalitis is suspected)
<i>Staff</i>
4. An adequately staffed, trained, motivated and paid active surveillance team. 5. Regular training and observation in the use of reliable and validated measures of adverse effects. 6. A motivated and adequately trained administrative structure should check each item of the work of the active surveillance team, and implement continuous quality improvement techniques. 7. Senior administrators should take a very active role in visiting, training, supervising, evaluating and rewarding all staff
<i>Surveillance</i>
8. The team should compile and continually update a complete listing of all vaccinees and their addresses. 9. Adequate transport to visit all patients in their home villages should be provided. 10. The team should arrange to see all vaccinees at appropriate times post-vaccination (day 0 to assess for anaphylaxis/hypersensitivity reactions; several times within days 0–10 for local and systemic reactions; and several times within the first 30 days for severe vaccinee reactions). 11. A medical team equipped to visit patients with potential adverse effects to assess the differential diagnosis (whether it is a yellow fever vaccine related event or not) and take an appropriate clinical history and draw laboratory tests. 12. Identify vaccinators not following sterile technique, and illegal vaccinators. 13. Identify lot or batch numbers with which serious adverse events appear to be associated. “Just in time” continuous surveillance should be used to report adverse events, as batches may be given to large numbers of individuals on the same day. 14. Avoid instituting vaccination campaigns where other vaccines are administered.

hospitals in Brazil who were on immunosuppressants and found no serious AEFIs. Pritchard et al. [68] surveyed 3000 members of a UK Guillain–Barré Support Group, and for the 1114 who returned questionnaires no serious AEFIs were identified.

3.7. Passive surveillance: children, pregnant females, HIV+ individuals

We identified two reports involving 35,270 children [74,75] and no serious AEFIs were proven. The data are heavily weighted (99%) by Cannon's [74] report from Nigeria. Cannon noted 35,000 17D vaccinations had been given in Lagos, Nigeria, and no serious reactions in infants had been reported. The Global Advisory Committee on Vaccine Safety (16–17 June 2010) [76] reviewed three cases of encephalitis after their mothers had received a first vaccination during the infant's first month of life but noted the mode of transmission has not been established. Mouchon et al. [75] reviewed data on 270 of 319 infants 6–12 months in Cameroon and noted no resulting consultations or mentions by the mother on the 30th day after vaccination.

We identified four reports for 138 pregnant women [77–80] and no serious AEFIs were reported. D'Acremont et al. [77] conducted a retrospective chart review of 131 pregnant women who had attended a travel clinic in Switzerland 1988–2000: only 6 were identified as having received yellow fever vaccine and there were no serious AEFIs. Nishioka Sde et al. [78] identified 39 pregnant women who had received 17D in Uberlândia, Brazil and no serious AEFIs were reported. Robert et al. [79] asked 11 European Network of Teratology Information Services to search their databases for exposure of pregnant females to yellow fever vaccine and 58 cases were followed up with no serious AEFIs. Tsai et al. [80] recorded that “about” 300,000 doses of 17DD and 100,000 doses of 17D-204 were administered in Trinidad and Tobago in 1989 and a survey of the seven largest hospitals suggested up to 1200 women received the vaccine unaware they were pregnant, and 35 mothers were identified by retrospective chart review who had received YFV after conception, but no serious AEFIs were recorded.

We identified six reports involving 191 HIV+ patients [81–86] and one review [49] of patients who were HIV+, and no serious AEFIs were proven. Goujon et al. [81] reported on 44 patients with CD4 lymphocyte counts over 200 at the Hôpital de l'Institut Pasteur, Paris, vaccinated with 17D 1988–1991, and no serious AEFIs were noted. Ho et al. [82] conducted a retrospective chart review on a random sample of 144 patients out of 3100 attending the HIV/AIDS clinic at the Hospital Las Clínicas, University of Sao Paulo, Brazil: 7 had received yellow fever vaccine and no AEFIs were recorded. Pacanowski et al. [83] reported on 103 patients who received 17D at the Travel Clinic of the Hôpital Saint Antoine, Paris, 2003–2007,

and no serious AEFIs were reported. Pistone et al. [84,87] identified 23 individuals (22 had a CD4 count above 200) vaccinated with 17D Centre Hospitalier Universitaire in Bordeaux 2000–2003 and no serious AEFIs were recorded. Receveur et al. [85] reported 2 individuals in France who received 17D and no serious AEFIs were reported. Tattevin et al. [86] identified 12 patients (mean CD4 cell count 561 ± 363 cells/mm³) at Pontchaillou Hospital, Rennes, France 1995–2002 and no serious AEFIs were reported. Veit et al. [49] reviewed the literature on serious AEFIs in HIV+ individuals after yellow fever vaccination and concluded that only one fatal case had been identified, and no specific yellow fever tests had been conducted.

4. Discussion

Problems in interpreting the results of these studies are their heterogeneity, administration of other vaccines, variations in the completeness of their active and passive surveillance methods, the multiple other possible pathogens that can present as encephalitis, hepatitis or multiple organ failure, and variations in the ability to test if yellow fever vaccine was implicated.

The studies are very heterogeneous by country, dates, number of participants, other vaccines administered, surveillance methods and testing. In rural and remote areas with minimal access to medical care many adverse reactions or deaths may not have been attributed to yellow fever vaccine or reported. The symptoms of encephalitis caused by yellow fever vaccine can also occur with bacteria, other viruses, or wild yellow fever, the symptoms of viscerotropic syndrome may occur in other causes of multi-organ failure, and those of anaphylaxis/hypersensitivity with other vaccines or allergens, and attributing causality may be very difficult without expert medical care and investigations. The fully documented reports in the literature are preponderantly from non-endemic countries, suggesting that the identification, diagnosis and reporting of cases is strongly influenced by whether an individual with a potential reaction to yellow fever vaccine presents to a secondary or tertiary care hospital which has the resources to assess the possibility of a vaccine reaction, take a comprehensive history, and perform appropriate tests to rule out the many competing differential diagnoses. A second layer of passive surveillance is the strong likelihood that physicians in endemic countries will have fewer resources and access to publish cases.

Many studies in the literature report event rates for yellow fever combined with other vaccines, making the interpretation of adverse events problematic. Adverse events after yellow fever vaccination are less frequent in those receiving a second vaccination, and most studies do not provide this crucial information. Only one RCT included a placebo group (Camacho 2005) [25] and although

some of the non-RCTs of pregnant females compare the vaccinated patients to a comparison group, the comparability of the groups is sometimes difficult to assess.

To improve the accuracy of reporting, all campaigns and programmes of vaccination should use active surveillance techniques (Table 4).

5. Conclusions

We identified 66 relevant studies: 24 used active, 17 a combination of passive and active (15 of which were pharmacovigilance databases), and 25 passive surveillance.

Ten pharmacovigilance databases contributed 107,621,154 patients, heavily weighted (94%) by the Brazilian database. Within this group the estimates for Australia were low at 0/210,656 for “severe neurological disease” and 1/210,656 for YEL-AVD, and also low for Brazil with 9 hypersensitivity events, 0.23 anaphylactic shock events, 0.84 neurologic syndrome events and 0.19 viscerotropic syndrome events/million doses. The five analyses of partly overlapping periods for the US VAERS database provided an estimate of 6.6 YEL-AVD and YEL-AND cases per million, and estimates between 11.1 and 15.6 of overall “serious adverse events” per million. The estimates for the UK were higher at 34 “serious adverse events” and also for Switzerland with 14.6 “neurologic events” and 40 “serious events not neurologic”/million doses.

Both the active and passive surveillance studies provided estimates lower than the pharmacovigilance databases. The active surveillance studies in general populations contributed 2,660,929 patients, heavily weighted (97.7%) by one large Brazilian study: there were no observed cases of viscerotropic or neurotropic disease, one of anaphylaxis and 26 cases of urticaria (hypersensitivity). We also identified four studies of infants and children ($n=2199$), four studies of pregnant women ($n=1334$), and one study of 174 HIV+, and no serious adverse events were observed.

Six passive surveillance studies of campaigns in general populations contributed 94,500,528 individuals, very heavily weighted (99%) by the Brazilian data, and providing an estimate of 0.51 serious AEFIs/million doses. Five retrospective reviews of hospital or clinic records included 60,698 individuals, heavily weighted (96%) by the data from the Hospital for Tropical Diseases, London, and no serious AEFIs were proven. Two studies included 35,723 children, four studies included 138 pregnant women, six studies included 191 HIV+ patients and there was one review of patients who were HIV+, and no serious AEFIs were proven.

The differences between the results for the databases are likely due to multiple factors: different definitions of serious adverse events, differences in the quality, application and supervision of surveillance mechanisms to identify cases, and marked differences in the availability of even simple laboratory tests. To prove that yellow fever vaccine is the causative agent requires sophisticated pathology, histopathology and amplicon sequencing using tests such as PCR amplification. Such sophistication is evident in the reports from Europe and some from Brazil.

To improve detection of serious adverse events by active surveillance studies and in pharmacovigilance databases (which use passive reports then actively follow them up) would require a careful history from each vaccinee concerning previous and current illnesses, medications, travel, other vaccines received in the past, previous yellow fever vaccination and biochemical and infectious diseases measures; staff regularly trained in the use of reliable and validated measures of adverse effects; a complete listing of all vaccines; assessment of all vaccinees (in person in the case of active surveillance studies) on the day of vaccination to assess for anaphylaxis/hypersensitivity reactions, several times within the first ten days for local and systemic reactions, and several times within the first 30 days for severe vaccine reactions, the ability to promptly

report adverse events as vaccine batches may be given to large numbers of individuals on the same day; and avoidance if possible of vaccination campaigns where other vaccines are administered.

Funding: At least 5 deaths were attributed to yellow fever during campaigns in Peru in 2007. The Global Advisory Committee on Vaccine Safety (GAVCS), therefore, requested that the WHO commission an independent systematic review of the safety of yellow fever vaccine. This independent commissioned systematic review was prepared for the WHO and GAVCS by a research team at the University of Calgary headed by Professor Roger Thomas. The systematic review was funded by The Global Alliance for Vaccines and Immunization (GAVI). The focal contact person for the WHO was Alejandro Costa, with Dr. Rosamund Lewis. There was extensive correspondence with the WHO focal person and Dr. Rosamund Lewis, with additional correspondence with Dr. Sergio Yactayo. The scientific independence of the researchers was at all times maintained. The sponsors did not participate in the collection, analysis or interpretation of data or in the writing of the report. **Contributors:** The following individuals executed these tasks: Writing the study Protocol and WHO Ethics approval (RET/DL); Literature searches (DL); Application of inclusion/exclusion criteria to abstracts (DL/WS/RET); Selection of full text studies for inclusion in review (DL/WS/RET); Reading, analysis and data entry from foreign language articles ($n=118$) (RET); assessment of risk of bias using Cochrane Collaboration criteria (RET/WS); data extraction from published studies (RET/DL/WS); Creation of initial versions of Excel, Access 2003 and Access 2007 databases of Adverse Events (RET); Development of ACCESS 2007 database, data analysis software and data analyses in ACCESS (DJ); Entering of data from published studies into ACCESS and 3 other specially created databases in Excel (RET/WS/DL); Statistical analyses and text (TW).

References

- [1] Barrett AD, Monath TP, Barban V, Niedrig M, Teuwen DE. 17D yellow fever vaccines: new insights. A report of a workshop held during the World Congress on medicine and health in the tropics, Marseille, France, Monday 12 September 2005. *Vaccine* 2007;25(15):2758–65.
- [2] Meeting of Global Advisory Committee on Vaccine Safety, 18–19 June 2008. *Wkly Epidemiol Rec* 2008;83(32):287–92.
- [3] Bae H-G, 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.
- [4] Guimard T, Minjolle S, Polard E, Fily F, Hervé H, Michelet C, et al. Incidence of yellow fever vaccine-associated neurotropic disease. *Am J Trop Med Hyg* 2009;81(6):1141–3.
- [5] Kelso JM, Mootrey GT, Tsai TF. Anaphylaxis from yellow fever vaccine. *J Allergy Clin Immunol* 1999;103(4):698–701.
- [6] Kitchener S. Viscerotropic and neurotropic disease following vaccination with the 17D yellow fever vaccine, ARILVAX. *Vaccine* 2004;22(17–18):2103–5.
- [7] Levy S. Centers for Disease Control and Prevention (CDC). Adverse events associated with 17D-derived yellow fever vaccination – United States, 2001–2002. *MMWR Morb Mortal Wkly Rep* 2002;51(44):989–93.
- [8] Lindsey NP, Schroeder BA, Miller ER, Braun MM, Hinckley AF, Marano N, et al. Adverse event reports following yellow fever vaccination. *Vaccine* 2008;26(48):6077–82.
- [9] McMahon AW, Eidex RW, Marfin AA, Russell R, Sejvar JJ, Markoff L, et al. Neurologic disease associated with 17D-204 yellow fever vaccination: a report of 15 cases. *Vaccine* 2007;25(10):1727–34.
- [10] Monath T, Cetron M, Teuwen D. Yellow fever vaccine. In: Plotkin SA, Orenstein WA, Offit PA, editors. *Vaccines*. 5th ed. Philadelphia: Saunders/Elsevier; 2008. p. 959–1056.
- [11] Struchiner CJ, Luz PM, Dourado I, Sato HK, Aguiar SG, Ribeiro JGL, et al. Risk of fatal adverse events associated with 17DD yellow fever vaccine. *Epidemiol Infect* 2004;132(5):939–46.
- [12] Vellozzi C, Mitchell T, Miller E, Casey CG, Eidex RB, Hayes EB. Yellow fever vaccine-associated viscerotropic disease (YEL-AVD) and corticosteroid therapy: eleven United States cases, 1996–2004. *Am J Trop Med Hyg* 2006;75(2):333–6.
- [13] Whittombury A, Ramirez G, Hernández H, Roper AM, Watermen S, Ticona M, et al. Viscerotropic disease following yellow fever vaccination in Peru. *Vaccine* 2009;27(43):5974–81.

- [14] Bonhoeffer J, Kohl K, Chen R, Duclos P, Heijbel H, Heininger U, et al. The Brighton Collaboration: addressing the need for standardized case definitions of adverse events following immunization (AEFI). *Vaccine* 2002;21(3–4):298–302.
- [15] Bonhoeffer J, Heininger U, Kohl K, Chen RT, Duclos P, Heijbel H, et al. Standardized case definitions of adverse events following immunization (AEFI). *Vaccine* 2004;22(5–6):547–50.
- [16] Gold MS, Gidudu J, Erlewyn-Lajeunesse M, Law B. Can the Brighton Collaboration case definitions be used to improve the quality of adverse event following immunization (AEFI) reporting? Anaphylaxis as a case study. *Vaccine* 2010;28(28):4487–98.
- [17] Bonhoeffer J, Bentsi-Enchill A, Chen RT, Fisher MC, Gold MS, Hartman K, et al. Guidelines for collection, analysis and presentation of vaccine safety data in surveillance systems. *Vaccine* 2009;27(April 6 (16)):2289–97.
- [18] Council for International Organizations of Medical Sciences (CIOMS). Reporting form for international reporting of adverse drug reactions. CIOMS 2011. Available from: URL: <http://www.cioms.ch>.
- [19] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Guidelines for clinical safety assessment (E2a-e). ICH 2011. Available from: URL: <http://www.ich.org>.
- [20] 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.
- [21] Oyelami SA, Olaleye OD, Oyejide CO, Omilabu SA, Fatunla BA. Severe post-vaccination reaction to 17D yellow fever vaccine in Nigeria. *Rev Roum Virol* 1994;45(1–2):25–30.
- [22] Nasidi A, Monath TP, Vandenberg J, Tomori O, Calisher CH, Hurtgen X, et al. Yellow fever vaccination and pregnancy: a four-year prospective study. *Trans R Soc Trop Med Hyg* 1993;87(3):337–9.
- [23] WHO Emerging and Other Communicable Diseases. District guidelines for yellow fever surveillance. Geneva: World Health Organization; 1998. Report No.: WHO/EPI/GEN/98.09.
- [24] Ambrosch F, Fritzell B, Gregor J, Jonas S, Kollaritsch H, Teulieres L, et al. Combined vaccination against yellow fever and typhoid fever: a comparative trial. *Vaccine* 1994;12(7):625–8.
- [25] Camacho LAB, Freire Mda S, Leal Mda LF, de Aguiar SG, do Nascimento JP, Iguchi T, et al. Reactogenicity of yellow fever vaccines in a randomized, placebo-controlled trial. *Rev Saude Publica* 2005;39(3):413–20.
- [26] Cavalanti DP, Salomao MA, Lopez-Camelo J, Pessoto MA. Campinas group of yellow fever immunization during P. Early exposure to yellow fever vaccine during pregnancy. *Trop Med Int Health* 2007;12(7):833–7.
- [27] Dick GWA, Horgan ES. Vaccination by scarification with a combined 17D yellow fever and vaccinia vaccine. *J Hyg* 1952;50(3):376–83.
- [28] Dick GWA. A preliminary evaluation of the immunizing power of chick-embryo 17D yellow fever vaccine inoculated by scarification. *Am J Hyg* 1952;55:140–53.
- [29] Edwan T. Yellow fever vaccination for the Jordanian peace keeping forces. *Jordan Med J* 2004;38(1):84–7, 109.
- [30] Fitzner J, Coulibaly 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.
- [31] Hahn RG. A combined yellow fever-smallpox vaccine for cutaneous application. *Am J Hyg* 1951;54:50–70.
- [32] Lang J, Zuckerman JN, Clarke P, Barrett P, Kirkpatrick C, Blondeau C. Comparison of the immunogenicity and safety of two 17D yellow fever vaccines. *Am J Trop Med* 1999;60(6):1045–50.
- [33] Lhuillier M, Mazzariol MJ, Zadi S, Le Cam N, Bentejac MC, Adamowicz L, et al. Study of combined vaccination against yellow fever and measles in infants from six to nine months. *J Biol Stand* 1989;17(January (1)):9–15.
- [34] Monath TP, Nichols R, Archambault WT, Moore L, Marchesani R, Tian J, et al. Comparative safety and immunogenicity of two yellow fever 17D vaccines (ARILVAX and YF-VAX) in a phase III multicenter, double-blind clinical trial. *Am J Trop Med Hyg* 2002;66(5):533–41.
- [35] 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.
- [36] Moss-Blundell AJ, Bernstein S, Shepherd WM, Langford DT, Ferris R, Kelly A. A clinical study of stabilized 17D strain live attenuated yellow fever vaccine. *J Biol Stand* 1981;9(4):445–52.
- [37] Osei-Kwasi M, Dunyo SK, Koram KA, Afari EA, Odoom JK, Nkrumah FK. Antibody response to 17D yellow fever vaccine in Ghanaian infants. *Bull World Health Organ* 2001;79(11):1056–9.
- [38] Panthier R, Husson RA. Yellow fever vaccination (17-D) and allergy. *Bull Soc Pathol Exot Filiales* 1957;50(1):23–8.
- [39] Papaïordanou P, Sato H, Freire M, Yamamura A, Gouveia F, Amaral E. Yellow fever vaccination during pregnancy. In: Abstracts of the interscience conference on antimicrobial agents and chemotherapy. 2001. p. 41.
- [40] Pfister M, Kürsteiner O, Hilfiker H, Favre D, Durrer P, Ennaji A, et al. Immunogenicity and safety of Berna-YF compared with two other 17D yellow fever vaccines in a phase 3 clinical trial. *Am J Trop Med* 2005;72(3):339–46.
- [41] Pivetaud JP, Raccourt CP, M'Bailara L, Le Vigouroux A, Le Bras M. Reactions to vaccination against yellow fever. *Bull Soc Pathol Exot Filiales* 1986;79(5 Pt 2):772–6.
- [42] Roche JC, Jouan A, Brisou B, Rodhain R, Fritzell B, Hannoun C. Comparative clinical study of a new 17D thermostable yellow fever vaccine. *Vaccine* 1986;4(3):163–5.
- [43] Smith HH, Penna HA, Paoliello A. Yellow fever vaccination with cultured virus (17D) without immune serum. *Am J Trop Med* 1938;1–18(5):437–68.
- [44] Soula G, Sylla A, Pichard E, Kodio B, Bentejac AC, Teulieres L, et al. A new combined vaccine against yellow fever and measles in infants aged 6 to 24 months in Mali. *Bull Soc Pathol Exot* 1991;84(5 Pt. 5):885–97.
- [45] Suzano CE, Amaral E, Sato HK, Papaïordanou PM. Campinas group on yellow fever immunization during P. The effects of yellow fever immunization (17DD) inadvertently used in early pregnancy during a mass campaign in Brazil. *Vaccine* 2006;24(9):1421–6.
- [46] Tauraso NM, Myers MG, Nau EV, O'Brien TC, Spindel SS, Trimmer RW. Effect of interval between inoculation of live smallpox and yellow-fever vaccines on antigenicity in man. *J Infect Dis* 1972;126(4):362–71.
- [47] Veit O, Niedrig M, Chapuis-Taillard C, Cavassini M, Mossdorf E, Schmid P, et al. Immunogenicity and safety of yellow fever vaccination for 102 HIV-infected patients. *Clin Infect Dis* 2009;48(5):659–66.
- [48] Smith HH, Penna HA, Paoliello A. Yellow fever vaccination with cultured virus (17D) without immune serum. *Am J Trop Med* 1938;1–18(5):437–68.
- [49] Veit O, Hatz C, Niedrig M, Furrer H. Yellow fever vaccination in HIV-infected patients. *HIV Therapy* 2010;4(1):17–26.
- [50] Review of adverse events reported following use of yellow fever vaccine – Canada, 1987–2000. *Can Commun Dis Rep* 2002;28(2):9–15.
- [51] From the Centers for Disease Control and Prevention. Adverse events associated with 17D-derived yellow fever vaccination – United States, 2001–2002. *JAMA* 2002;288(20):2533–5.
- [52] Bentaïcourt S, Valsecia M, Perez A, Bergman M, Bignone K. Adverse events supposedly attributable to vaccination of yellow fever. *Drug Safety* 2008;31(10):942.
- [53] Fernandes GC, Camacho LA, Sa Carvalho M. Surveillance system of vaccine adverse events and local data analysis – the experience in a middle-sized city in Brazil, 1999–2001. *Vaccine* 2005;23(17–18):2349–53.
- [54] Fernandes GC, Camacho LA, Sa Carvalho M, Batista M, de Almeida SM. Neurological adverse events temporally associated to mass vaccination against yellow fever in Juiz de Fora, Brazil, 1999–2005. *Vaccine* 2007;25(16):3124–8.
- [55] Khromava AY, Eidex RB, Weld LH, Hohl 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.
- [56] Lawrence G, Menzies R, Burgess M, McIntyre P, Wood N, Boyd N, et al. Surveillance of adverse events following immunisation: Australia, 2000–2002. *Commun Dis Intell* 2003;27(3):307–23.
- [57] 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.
- [58] 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.
- [59] Martins RdeM, Maia MdeLdeS, dos Santos EM, Cruz RLdeS, dos Santos PRG, Carvalho SMD, et al. Yellow fever vaccine post-marketing surveillance in Brazil. *Procedia Vaccinol* 2010;2(2):178–83.
- [60] Schumacher Z, Bourquin C, Heininger U. Surveillance for adverse events following immunization (AEFI) in Switzerland-1991–2001. *Vaccine* 2010;28(24):4059–64.
- [61] Souayah N, Nasar A, Suri MFK, Qureshi AI. Guillain-Barre syndrome after vaccination in United States. A report from the CDC/FDA Vaccine Adverse Event Reporting System. *Vaccine* 2007;25(29):5253–5.
- [62] Diop Mar I, Niang I, Guicheney A, Berne C, Collomb H, Rey M, et al. Encephalitis following anti-yellow fever vaccination (from 248 cases observed at Dakar in 1965). *Ann Pediatr (Paris)* 1967;14(3):181–91.
- [63] Diop Mar I, Ayats H, Rey M. The problem of post-yellow fever vaccination encephalitis. *Bull Soc Med Afrique Noire Langue Francaise* 1970;15(3):468–79.
- [64] Vasconcelos PFC, Luna EJ, Galler R, Silva LJ, Coimbra TL, Barros VLRS, et al. Serious adverse events associated with yellow fever 17DD vaccine in Brazil: a report of two cases. *Lancet* 2001;358(9276):91–7.
- [65] World Health Organization. Prevention and control of yellow fever in Africa. Geneva: World Health Organization; 1986.
- [66] Da Mota LMH, Oliveira ACV, Lima RAC, Dos Santos-Neto LL, Tauil PL. Vaccination against yellow fever among patients on immunosuppressors with diagnoses of rheumatic diseases. *Rev Soc Bras Med Trop* 2009;42(1):23–7.
- [67] Kouwenaar W. The reaction to yellow fever vaccine (17D), particularly in allergic individuals. *Doc Med Geogr Trop* 1953;5(1):75–84.
- [68] Pritchard J, Mukherjee R, Hughes RAC. Risk of relapse of Guillain-Barre syndrome or chronic inflammatory demyelinating polyradiculoneuropathy following immunisation. *J Neurol Neurosurg Psychiatry* 2002;73(3):348–9.
- [69] Roodyn L. Encephalitis after yellow fever vaccination. *Br Med J* 1954;2(4898):1226.
- [70] Wolga J, Rodhain F, Hannoun C, Dodin A, Fritzell B, Loucq C, et al. Evaluation of thermostable yellow fever vaccine from the Pasteur Institute on international travellers. *J Biol Stand* 1986;14(4):289–95.
- [71] Haas L. Encephalitis after yellow-fever vaccination. *Br Med J* 1954;2(4894):992–3.
- [72] Scott LG. Encephalitis after yellow-fever vaccination. *Br Med J* 1954;2(4896):1108.
- [73] Smith JH. Encephalitis in an infant after vaccination with 17 D yellow fever virus. *Br Med J* 1954;2(4892):852.

- [74] Cannon D. Encephalitis after yellow fever vaccination. *Br Med J* 1955;1(4921):1090.
- [75] Mouchon D, Pignon D, Vicens R, Thanh T-H, Tekaia F, Teulières L, et al. The combined measles-yellow fever vaccination in African infants aged 6 to 10 months. *Bull Soc Pathol Exot* 1990;83(4):537–51.
- [76] Anonymous. Global advisory committee on vaccine safety, 16–17 June 2010. *Wkly Epidemiol Rec* 2010;85(30):285–91.
- [77] D'Acremont V, Tremblay S, Genton B. Impact of vaccines given during pregnancy on the offspring of women consulting a travel clinic: a longitudinal study. *J Travel Med* 2008;15(2):77–81.
- [78] Nishioka Sde A, Nunes-Araujo FR, Pires WP, Silva FA, Costa HL. Yellow fever vaccination during pregnancy and spontaneous abortion: a case-control study. *Trop Med Int Health* 1998;3(1):29–33.
- [79] Robert E, Vial T, Schaefer C, Arnon J, Reuvers M. Exposure to yellow fever vaccine in early pregnancy. *Vaccine* 1999;17(3):283–5.
- [80] Tsai TF, Paul R, Lynberg MC, Letson GW. Congenital yellow fever virus infection after immunization in pregnancy. *J Infect Dis* 1993;168(6):1520–3.
- [81] Goujon C, Tohr M, Feuillie V, Coulaud P, Dupont B, Sansonetti P. Good tolerance and efficacy of yellow fever vaccine among carriers of human immunodeficiency virus. *J Travel Med* 1995;2(2):145.
- [82] Ho YL, Enohata T, Lopes MH, De Sousa Dos SS. Vaccination in Brazilian HIV-infected adults: a cross-sectional study. *AIDS Patient Care STDs* 2008;22(1):65–70.
- [83] Pacanowski J, Campa P, Dabrowska M, Lacombe K. Antibody response and safety of yellow fever vaccination in HIV infected patients. 48th Annual ICAAC (Washington, DC, October 25–28, 2008) 2008; Poster No. G 392.
- [84] Pistone T, Verdier CH, Receveur MC, Ezzedine K, Lafon ME, Malvy D. Immunogenicity and safety of yellow fever vaccine in HIV-living travelers, France, 2005. (Special Issue: Travelers' health 2007.). *Bull Epidemiol Hebd* 2007;25/26:238–40.
- [85] Receveur MC, Thiebaut R, Vedy S, Malvy D, Mercie P, Bras ML. Yellow fever vaccination of human immunodeficiency virus-infected patients: report of 2 cases. *Clin Infect Dis* 2000;31(3):E7–8.
- [86] Tattevin P, Depatureaux AG, Chaplain TM, Dupont M, Souala F, Arvieux C, et al. Yellow fever vaccine is safe and effective in HIV-infected patients. *AIDS* 2004;18(5):825–7.
- [87] Pistone T, Verdier CH, Receveur MC, Ezzedine K, Lafon ME, Malvy D. Immunogenicity and tolerability of yellow fever vaccination in 23 French HIV-infected patients. *Curr HIV Res* 2010;8(September (6)):461–6.