

# Reporting Rates of Yellow Fever Vaccine 17D or 17DD-Associated Serious Adverse Events in Pharmacovigilance Data Bases: Systematic Review

Roger E. Thomas<sup>\*,1</sup>, Diane L. Lorenzetti<sup>2</sup>, Wendy Spragins<sup>3</sup>, Dave Jackson<sup>3</sup> and Tyler Williamson<sup>4</sup>

<sup>1</sup>Department of Family Medicine, University of Calgary, G012, Health Sciences Centre, 3330 Hospital Drive NW, Calgary, Alberta, T2N 4N1, Canada

<sup>2</sup>Department of Community Health Sciences, Faculty of Medicine, University of Calgary, 3rd Floor, TRW, 3280 Hospital Drive NW, Calgary Alberta, T2N 4Z6, Canada

<sup>3</sup>Independent Research Consultant, University of Calgary, Calgary, Alberta, Canada

<sup>4</sup>Departments of Community Health Sciences and Family Medicine, 3280 Hospital Drive NW, Calgary, Alberta, T2N 4Z6, Canada

**Abstract:** *Purpose:* To assess the reporting rates of serious adverse events attributable to yellow fever vaccination with 17D and 17DD strains as reported in pharmacovigilance databases, and assess reasons for differences in reporting rates.

*Methods:* We searched 9 electronic databases for peer reviewed and grey literature (government reports, conferences), in all languages. Reference lists of key studies were also reviewed to identify additional studies.

*Results:* We identified 2,415 abstracts, of which 472 were selected for full text review. We identified 15 pharmacovigilance databases which reported adverse events attributed to yellow fever vaccination, of which 10 contributed data to this review with about 107,600,000 patients (allowing for overlapping time periods for the studies of the US VAERS database), and the data are very heavily weighted (94%) by the Brazilian database. The estimates of serious adverse events form three groups. 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 provide an estimate of 3.6/cases per million YEL-AND in one analysis and 7.8 in another, and 3.1 YEL-AVD in one analysis and 3.9 in another. The estimates for the UK used only the inclusive term of "serious adverse events" not further classified into YEL-And or YEL-AND and reported 34 "serious adverse events." The Swiss database used the term "serious adverse events" and reported 7 such events (including 4 "neurologic reactions") for a reporting rate of 25 "serious adverse events"/million doses.

*Conclusions:* Reporting rates for serious adverse events following yellow fever vaccination are low. Differences in reporting rates may be due to differences in definitions, surveillance system organisation, methods of reporting cases, administration of YFV with other vaccines, incomplete information about denominators, time intervals for reporting events, the degree of passive reporting, access to diagnostic resources, and differences in time periods of reporting.

**Keywords:** Pharmacovigilance, risk of bias, serious adverse effects, systematic review, yellow fever, yellow fever 17D and 17DD vaccine.

## INTRODUCTION

Yellow fever (YF) is a viral disease transmitted by mosquitoes in the tropical areas of 45 endemic African and Latin America countries with a population of more than 900 million, and occurs in both urban and rural areas. Yellow fever has a high mortality often exceeding 60%.

Yellow fever vaccination can cause serious adverse events which have reported mortality rates from 20% to 80% [1], and include neurologic and viscerotropic syndromes and anaphylaxis. Common signs of neurological syndromes due to both yellow fever and yellow fever vaccine are those of encephalitis, myelitis, or encephalomyelitis (ADEM).

Common signs of viscerotropic syndrome due to both yellow fever and yellow fever vaccine include:

- fever, headache, nausea, vomiting (early disease stage 3-6 days after mosquito bite)
- sudden onset of fever, headache, nausea, vomiting, chills, backache, generalised muscle pain, conjunctival injection (red eye), dark urine, and jaundice (these are the classic symptoms 4-10 days post onset)
- and finally brief improvement followed by jaundice, vomiting blood, bleeding from gums, nose or GI tract, blood in urine, decreased/no urine production, shock and death (these are the symptoms of the late stage 7-10 days post onset) [2].

Because the signs and symptoms of yellow fever are shared by many other diseases, including bacterial

\*Address correspondence to this author at the Department of Family Medicine, University of Calgary, G012, Health Sciences Centre, 3330 Hospital Drive NW, Calgary, Alberta, T2N 4N1, Canada; Tel: 403 210 9208; Fax: 403 270 4329; E-mail: rthomas@ucalgary.ca

meningitis, malaria and viral hepatitis, data on the actual number of yellow fever cases are difficult to determine.

An outbreak of yellow fever can go undetected because the signs and symptoms of yellow fever are similar to viral hepatitis, malaria, leptospirosis, typhus, Ebola hemorrhagic fever and other hemorrhagic fevers. It is difficult for health workers to make a definitive diagnosis based on the signs and symptoms alone. Mild cases may go undetected because the patient is likely to be treated at home and does not seek care in a health facility [2].

The World Health Organization estimates that only 1-2% of cases are reported, and that there are approximately 200,000 new cases each year [2] with an estimated 30,000 possible deaths annually, 90% of which are in Africa [3].

Yellow fever may present in intermittent unpredictable epidemics. There were expansions in the areas experiencing yellow fever in the 1950's in Central America and in the 1960's and 1980's in West Africa [4]. There are seven genotypes of yellow fever and outbreaks in Kenya 1992-3 and Sudan in 2003 and 2005 involved the re-emergence of a yellow fever genotype that had not been detected in the

previous 40 years [5]. Most of the population at risk remains unvaccinated, and in Africa there is a wide range of intermediate hosts as well as human to human transmission [5]. It appears that yellow fever is re-emerging as a threat.

Yellow fever vaccine from 17D and 17DD strains has very low reported rates of adverse events, as evidenced by the more than 600 million doses distributed since 1939. However, there are reports of serious adverse events after yellow fever vaccine [6-17] and there is a need to determine the rates of adverse events and serious adverse events and identify risk factors that could also increase the risk of adverse events for certain populations, such as infants and children, pregnant females, immunosuppressed patients, and HIV positive individuals. Current evidence suggests that host factors and activation/modulation of the immune system may be related to adverse events [18].

Our research objective was to assess the reporting rates of serious adverse events following yellow fever vaccinations as reported in pharmacovigilance databases (Table 1), examine methods of data collection and adjudication of cases, and assess reasons for any differences in their estimated rates of serious adverse events.

**Table 1. Pharmacovigilance Reports of Serious Adverse Events Attributed to 17D and 17DD Yellow Fever Vaccine<sup>1</sup>**

| Author                             | Database                                         | Doses Administered                                                                     | Serious Adverse Events                                                                                                   | Serious Adverse Events Rate and 95% Confidence Interval/Million Doses <sup>2</sup>                             | Other Computations by the Authors: Rate/Million Doses            |
|------------------------------------|--------------------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| Lawrence (2003, 2004) <sup>2</sup> | Australian ADRAAC database 1993-2002             | 210,656                                                                                | 0 "severe neurological disease", 1 YEL-AVD                                                                               |                                                                                                                |                                                                  |
| Martins (2010)                     | Brazil National Immunizations Program, 2000-2009 | 101,564,083                                                                            | 26 viscerotropic cases (21 from Brazil, 5 other countries which used 17DD) of which 19 confirmed, 4 probable, 3 suspect) | AVD 0.19 (0.11 to 0.29)                                                                                        | hypersensitivity 9<br>anaphylactic shock 0.23<br>neurologic 0.84 |
| Schumacher (2010)                  | Swiss Government SFOPH organisation, 1991-2001   | 280,000 (This number is not reported by the authors but back-calculated from the rate) | 7 "serious AEFI" (including 4 neurologic reactions)                                                                      | 25 (10 to 52)                                                                                                  | Serious adverse events 25 (95% CI 10 to 52)                      |
| Monath (2005) <sup>3</sup>         | ARILVAX brand of 17D, UK                         | 1,043,415                                                                              | 34 "serious adverse events" not further classified                                                                       |                                                                                                                |                                                                  |
| Khromava (2005) <sup>4</sup>       | US VAERS 1990-2002                               | 2,230,760                                                                              | 8 AND, 7 AVD (civilian cases)                                                                                            | AND 3.6 (1.6 to 7.1)<br>AVD 3.1 (1.3 to 6.5)                                                                   |                                                                  |
| Lindsey (2008)                     | VAERS 2000 to 2006                               | 1,534,170                                                                              | 12 YEL-AND, 6 YEL-AVD, 28 anaphylaxis, 4 deaths                                                                          | AND: 7.8 (4.0 to 13.7)<br>AVD: 3.9 (1.4 to 8.5)<br>Anaphylaxis: 18.3 (12.1 to 26.4)<br>Death: 2.6 (0.7 to 6.7) |                                                                  |
| Martin (2001)                      | US VAERS 1990 to 1998                            | 1,443,686                                                                              | 16 "systemic adverse events (multisystemic or neurologic)"                                                               | 11.1 (6.3 to 18.0)                                                                                             |                                                                  |

YEL-AND = yellow fever associated neurological disease; AVD = yellow fever associated viscerotropic disease

<sup>1</sup>We have computed rates and 95% Confidence Limits per million doses based on the authors' reported numbers.

<sup>2</sup>For 15/42 cases YFV was the only vaccine involved, and it is not stated whether the events refer to the 15 or to the 42 cases. There were 9 "serious systemic events," 0 "severe neurological disease," and 1 YEL-AVD (fatal).

<sup>3</sup>190 adverse events were reported, and 36 classified as serious adverse events. The rate may be an underestimate because 24 of the 190 events were not classified (13 not from the UK, 6 < 15 years, 5 age not known).

<sup>4</sup>The studies by Souyah (2007) and Vellozzi (2006) were also of the VAERS database, but contributed no data additional to the studies by Martin (2001), Khromava (2005) and Lindsey (2008).

## METHODS

We searched 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 from the authors. The searches included all languages with no date limits. Web of Science Citation Search and PubMed's Related Articles features 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.

Two reviewers independently read all titles, abstracts and the full text articles to assess if they reported data from pharmacovigilance databases on serious yellow fever vaccination adverse events. Disagreements were discussed until consensus was reached.

## RESULTS

### Literature Search

We identified 2,415 abstracts, of which 472 were selected for full text review. We identified 15 studies of pharmacovigilance databases. Ten provided data for this review (2 from Australia, 1 each from Brazil, the UK and Switzerland, and 5 from the US).

**Pharmacovigilance databases: definitions of serious adverse events, methods of data collection, data quality assessment, and results** (all rates have been converted to cases/million vaccinations).

These databases are designed to receive reports of adverse events after all vaccinations. Problems in assessing adverse events after yellow fever vaccination in their reports are that patients may have received multiple vaccines, and databases use different terms such as "serious adverse events" or "systemic adverse events" and some do not break these down further into the yellow fever specific adverse events of YEL-AND and YEL-AVD.

### Australia (17D Vaccine)

**Lawrence (2004) [19]** reviewed the Australian ADRAC database for 1993-2002, which uses "spontaneous reports," i.e. passive surveillance. Cases were classified as having a 'systemic' adverse event or 'other' adverse event. The 'systemic events' were then classified as neurological or multi-systemic. The definition of neurological events was wider than other databases (new onset seizures, encephalitis, myelitis, altered mental status, focal cranial or peripheral neurological deficits, paresthesia, vertigo, +/- headache) as was also the definition of multi-systemic events (myalgia, arthralgia, impaired hepatic function, respiratory distress, nausea, vomiting, impaired renal function, +/- fever). Other adverse events were classified as mild non-specific (headache or dizziness without other symptoms or signs),

hypersensitivity (rash, urticaria, +/- fever, anaphylaxis, angioedema), or local reaction (localised pain, swelling, erythema or warmth at the injection site). Events were classified independently by two authors.

Lawrence noted 42 reports of adverse events for patients who received yellow fever vaccine and assessed 26 cases as "systemic," 9 as "serious systemic," none as "severe neurological disease," and 1 as a fatal case of YEL-AVD. Fifteen of the reports involved only yellow fever vaccine. These reports are not further described, and only the one case of YEL-AVD can be definitely ascribed to this group. Lawrence computed the total number of 210,656 doses for the period 1993-2002 by extrapolation from Sanofi-Pasteur sales for 1999-2002 (the only manufacturer who sold yellow fever vaccine in Australia during this period), and extrapolated the age distribution of vaccinees for 1992-2002 from a 15% sample of vaccine clinics for 1999-2002. Lawrence computed rates based on the 42 reports but we have instead computed a reporting rate based on the 15 cases in which only 17D was administered: 0/210,656 for "severe neurological disease," 1/210,656 for YEL-AVD, and the remaining 14 cases are not further described. The definition of a systemic adverse event was one occurring within two weeks of vaccination, which may understate the number of cases of neurologic or viscerotropic syndrome.

Lawrence commented:

The study had some limitations. Cases were identified through passive surveillance and are subject to the biases inherent in systems that rely on passive reporting, including the possibility of age-related reporting biases. The case definitions from the ADRAC data were more sensitive than those used in the USA study because the duration of symptoms could not be used as part of the [ADRAC] case definition. ...YF vaccinees had often received other vaccines at the same time...[19]

**Lawrence (2003) [20]** reviewed the Australian ADRAC database from 1 January 2000 to 30 September 2002. As this overlaps with his 2004 study, it is not reported in detail. The authors commented about the effects of passive surveillance:

The AEFI reporting rates cannot be interpreted as true incidence rates. Like all passive surveillance data, AEFI data are subject to under-reporting, over-reporting and reporting biases that are difficult to measure. There is under-reporting of less serious adverse events and of those sustained by adults. In contrast, there is over-reporting of serious events *coincidentally* associated with the timing of immunisation. There are a wide range of reasons why a reported AEFI might be assigned a 'possible' causality rating including insufficient information, the existence of a plausible alternative explanation or more than one vaccine or drug being administered at a time, as is frequently the case in infants and the elderly. The causality rating assigned to each AEFI record describes the likelihood that a suspected vaccine(s) was associated with the

reported adverse event at the level of the individual patient. This is not the same as the epidemiological concept of 'causality', which applies at the population level. Specific epidemiological studies are required to investigate the broader question of whether a vaccine is causally associated with a specific adverse event at the population level [20].

### Brazil (17DD)

**Martins (2010) [21]** assessed yellow fever vaccine-related events in Brazil from 2000 to 2009 as reported to the Ministry of Health. Brazil has a National Immunization Program and uses the WHO Manual for Detection of Serious Adverse Events after YFV and the CDC classification. There is a multi-level reporting system from the 30,000 health centres, and evaluation at state then national levels, with electronic adverse events databases shared with the manufacturer Bio-Manguinhos' Pharmacovigilance Unit, which also receives complaints from customers. There is a manual on AEFIs for intermediate level health professionals and a Guideline for the Investigation of Serious Adverse Events. State and national laboratories can provide pathology, histopathology, immunohistochemistry, cell culture and yellow fever vaccine amplicon testing. There are also sentinel hospitals charged with the detection of icterohemorrhagic febrile syndromes (yellow fever, VD, dengue, hantavirus, leptospirosis, meningococcal infection, malaria, rickettsial infections, typhoid fever, Brazilian purpura fever, and other arbovirus infections) with compulsory and immediate reporting. The database is by far the largest of any country. During the reporting period, 101,564,083 17DD doses were given, and a reporting rate of 9 cases of hypersensitivity, 0.23 of anaphylactic shock, 0.84 of yellow fever vaccine-associated neurologic syndrome and 0.19 of viscerotropic syndrome/million doses were computed. Martins actually reported 26 cases of viscerotropic syndrome with 21 from Brazil and 5 from neighbouring countries where the Bio-Manguinhos 17DD vaccine was also sold, and of the 26 cases 19 were reported as confirmed, 4 probable and 3 suspect [Martins' in his table 1 reports 20 cases for Brazil, but groups together the confirmed, probable and suspect cases, which cannot be separated].

The authors commented:

This system is not homogeneous, and has different sensitivities across the country. There is also a good capability for investigation of serious adverse events through a network of state laboratories and reference laboratories at national level. Cases are discussed at national level for final classification [21].

### Switzerland (17D)

**Schumacher (2010) [22]** evaluated reports of post-vaccination adverse events to the Swiss Government Federal Office of Public Health (SFPOH) 1991-2001. The law requires physicians to report adverse vaccination events that:

..."(a) occurred in reasonable temporal association (i.e. within 8 weeks after immunization), (b) no other plausible cause explained the event, and (c) it fulfilled one or more of the following criteria: it is serious, previously unknown to occur after immunization, or is the main cause for a physician visit.

Reports of AEFI should contain the following information in a standardized fashion: date of report, age and sex of the patient, kind and lot number(s) of vaccine(s) used, description of the adverse event, time interval after immunization, duration of the event, and any additional remarks from the reporter, e.g. final outcome of the AEFI." [22]

The SFPOH divided the database by vaccine received and by multiple vaccines, then within each vaccine subdivided reactions by "organ system" as neurological (e.g. headache, convulsion), allergic (e.g. generalized urticaria, anaphylactic reactions), general systemic (e.g. fever, flu like symptoms), and local reactions (e.g. redness, swelling or pain at the injection site). Schumacher and his two co-authors analysed the data for all vaccines, and attributed the reported AEFIs to the vaccine which most likely caused the event, using the WHO classification for causal link (unclassifiable, unrelated, unlikely, possible, probable, or very likely/certain) and for severity: non-serious (mild severity), non-serious (moderate severity), and serious (severe). The definition of severe was: "any untoward medical occurrence that results in death, hospitalization or prolongation of hospitalization, persistent or significant disability/incapacity, or is life threatening."

They commented for all vaccine events 1991-2001 that:

Sufficient information for seriousness and severity assessment was available in 1008 (99.5%) of AEFI reports. Of these, 787 (78.1%) were non-serious, 298 (29.4%) mild, and 220 (21.8%) were serious and severe, including 10 deaths, 89 hospitalizations and 10 events leading to permanent disability [22].

Fifteen events were attributed to yellow fever vaccine, of which 11 were assessed as general systemic reactions, 4 as neurologic reactions, and none as allergic reactions. In a separate classification of the severity of the 15 events, 7 were assessed as serious, 7 as moderate and 1 as mild. For all 15 events the authors computed a reporting rate of 55 cases (95%CI = 31 to 90)/million doses, and for the seven "serious events" a rate of 25 (95% CI = 10 to 52)/million doses. The authors do not provide the total number of doses of yellow fever vaccine for the period, but we estimate 280,000 back-calculated from the rate.

The Swiss database received reports about all vaccines, and Schumacher experienced difficulty attributing causality for the deaths to vaccines:

Unfortunately, little information was available on diagnostic procedures applied to exclude other possible etiologies of most AEFI, which

explains the comparatively high proportion of events possibly related to immunization.

One percent of all AEFI in our study were deaths, which was one death per study year, none of them with very likely or certain causal relationship to the precedent immunization ... Two further deaths followed 7 and 21 days after yellow fever immunization, respectively. Underlying diseases were cholestatic hepatitis with hepatic necrosis in a 54 year old male and drug-related hepatitis in a 54 year old male. These two deaths were assessed as possibly related to immunization, as they occurred in plausible time intervals after immunization [22].

### UK (17D)

**Monath (2005) [23]** assessed serious AEFIs to the ARILVAX brand of 17D in the UK 1995-1999. Definitions of adverse events were broader than for most other databases: neurologic adverse events were defined as new onset seizures, encephalitis, myelitis, altered mental status, focal cranial or peripheral neurological deficits, Guillain-Barré syndrome, paresthesiae, vertigo, or headaches, and multisystemic events were defined as myalgias, arthralgias, rhabdomyolysis, elevated transaminases, respiratory distress, nausea, vomiting, diarrhea, nephropathy, disseminated intravascular coagulation, and fever. Headache alone did not qualify as an adverse neurologic event. Adverse events were sought from two sources: the UK Medicines and Healthcare Products Regulatory Agency, and the Safety Department of the Manufacturer of ARILVAX. Three investigators independently assessed the events recorded on forms from the Council for the International Organization of Medical Sciences, and arbitrated them with the VAERS definitions: if more than one category was applicable the most serious category was used, and events were excluded for which a different diagnosis was available. Systemic events were classified as neurologic or multisystemic reactions, and other adverse events were defined as hypersensitivity, local reactions and nonspecific events (dizziness, headache, nausea).

One hundred and ninety adverse events were reported and 87 were excluded (63 not related to YFV, 13 not from the UK, 6  $\leq$  15 years of age, 5 age not known). Of the remaining 101 reports 36 were classified as serious adverse events. The number of doses of ARILVAX 17D for the period was 1,043,415, yielding a reporting rate of 34 serious adverse events/million doses. The "serious adverse events" are not further classified into neurologic, multisystemic or "other serious adverse events."

### US VAERS Database (17D)

There are 5 studies of the VAERS data base, with partly overlapping time periods.

**Martin (2001) [24]** assessed cases reported to the US VAERS database between 1990 and 1998. Reliable denominators were not available for military personnel and children less than 15 years of age and these groups were

excluded. Vaccine adverse events were classified as neurologic (Guillain-Barré syndrome, new onset seizures, encephalitis, myelitis, altered mental status, focal cranial or peripheral neurologic deficits, paresthesias, vertigo, headaches [headaches alone were not sufficient for a neurologic diagnosis]), multisystemic (myalgias, arthralgias, rhabdomyolysis, elevated transaminases, respiratory distress, nausea, vomiting, diarrhea, nephropathy, disseminated intravascular coagulation, +/- fever), neurologic/systemic uncomplicated (rapid clinical recovery in < 72 hours), nonspecific events without other focal finding, hypersensitivity, local reaction, or unrelated to vaccine. Systemic adverse events were defined as neurologic or multisystemic. Reports were independently reviewed by three physicians, who identified 35 systemic adverse events (in 16 of which only yellow fever vaccine had been given), and 36 "other adverse events" (uncomplicated neurologic/systemic, hypersensitivity or local reactions). Aventis Pasteur provided vaccine sales for 1995-9 (YF-VAX 17D vaccine was the only vaccine authorised for use in the US at that time) and by extrapolation 1,443,686 doses were sold to civilian purchasers for the period 1990-1998. Martin reported the rates for the 35 cases in which other vaccines were administered with yellow fever vaccine, but we estimated the reporting rate for the 16 events in which yellow fever vaccine alone was administered as 11.1 (95% CI: 6.3 to 18.0) "systemic adverse events"/million doses.

Martin commented:

Rates calculated from VAERS data have to be interpreted with caution because of the problems inherent in a passive reporting system. Estimates of adverse events based on VAERS reports are likely to underestimate actual events. ... Age-related reporting bias may have influenced our results. ... Another important limitation is that the estimated age distribution of travellers from the GeoSentinel clinics receiving vaccine in 1998 was assumed to apply for the entire study (1990 to 1998) and to be generalizable to the entire United States. However, if as many suspect, the proportion of elderly travelers has increased in recent years, this extrapolation will have overestimated the number of older travelers ... We excluded data on children < 15 years of age .... Also, the calculation of denominators relied on assuming that the increase in vaccines administered between 1995 and 1996 held for 1990 to 1994. ... An additional limitation is that the age-specific SyAEs to YF vaccine may reflect an age related response to vaccines in general or an increased amount of background illness in the elderly [24].

For all these reasons we refrained from reporting Martin's detailed calculations.

**Khromava (2005) [25]** reviewed events reported 1990-2002. An adverse serious event was defined as resulting in death, life threatening illness, inpatient hospitalisation, prolongation of existing hospitalisation, or persistent or significant disability. VAERS obtains follow up data on the event, other vaccines administered and the recipient's

medical history, and arbitration is by the Yellow Fever Vaccine Safety Working Group. Serum or CSF samples are tested for yellow fever vaccine for YEL-AVD and YEL-AND cases.

An estimated 2.2 million doses were purchased by civilian organizations, and there were 465 civilian cases, with 430 non-serious, 7 YEL-AVD and 8 YEL-AND cases. We estimated a reporting rate of 3.6 YEL-AND (95% CI: 1.6 to 7.1) and 3.1 YEL-AVD (95% CI: 1.3 to 6.5) civilian cases/million doses. In only 26% of cases was yellow fever the only vaccine administered, but YEL-AVD and YEL-AND are unique to yellow fever and so it is appropriate to attribute them to the effects of yellow fever vaccine. There were 257 military cases, with 245 non-serious, 1 YEL-AVD and 2 YEL-AND cases. The military purchased 7.4 million doses but because they may have stockpiled and ultimately not use many doses, we decided not to compute a military estimate.

**Lindsey (2008) [12]** reviewed adverse events reported to the US VAERS database 2000 to 2006. YF-VAX 17D vaccine manufactured by Sanofi Pasteur was the only vaccine authorised for use in the US at that time. Reports could be submitted by the manufacturer, vaccine administrators, recipients, or family members. Serious adverse events were defined as death, life-threatening illness, hospitalization, prolongation of an existing hospitalization, permanent disability, or other medically important condition. Serious adverse events were “routinely followed up to obtain additional information.”

We disentangled the cases in Lindsey’s various tables as follows: Lindsey reported 660 cases in which yellow fever was given either alone or with other vaccines and there were 12 YEL-AND, 6 YEL-AVD and 28 cases of anaphylaxis. For the 190 cases in which only 17D was given, there were 24 serious adverse events: 7 life-threatening illnesses, 21 hospitalisations, 1 prolongation of a hospitalisation and 1 death. For the 470 adverse events in which 17D was given in combination with other vaccines there were 48 serious adverse events (14 life-threatening illnesses, 37 hospitalisations, 4 prolongations of a hospitalisation, 7 cases of permanent disability, and 3 deaths). All YEL-AVD and YEL-AND cases occurred after primary yellow fever vaccinations. Because Lindsey’s table 1 reports 24 serious adverse events for yellow fever vaccine, and the 12 YEL-AND and 6 YEL-AND cases must by definition be included in this group, we decided to accept 24 as the total of serious adverse events. Lindsey accepted reports of adverse events for up to 60 days after YF vaccination: the usual time limit is up to 30 days, but as YEL-AVD and YEL-AND cases occur within 30 days, this change in the reporting interval definitely has no effect on the number of such cases identified.

The 28 cases of anaphylaxis were classified by Lindsey thus:

... reports were classified as probable anaphylactic reactions if the reaction occurred within 4h of vaccine administration and included at least one dermatologic symptom coding term (urticaria, flushing, angioedema, pruritus, rash) and at least one respiratory

symptom coding term (dyspnea, bronchospasm, pharyngeal edema, wheezing, throat tightness, dysphonia). In addition, the case definition for anaphylaxis developed by the Brighton Collaboration was also used. However, to allow for comparison with previously published reports of anaphylaxis following YF vaccine administration, the former definition was used in the bulk of this paper, except where otherwise noted [12].

The inconsistent use of the Brighton Collaboration criteria [26-29] makes it difficult to assess the author’s decisions about classification. Lindsey classified 28 events as probable anaphylactic reactions, of which 20 occurred in vaccinees who had received more than one vaccine. When the authors applied the Brighton anaphylaxis case definition, 33 reports met the criteria for either Level 1 or Level 2 of diagnostic certainty (however, only 28 cases are listed in table 3).

Lindsey computed the denominator as follows:

The number of YF-VAX doses purchased by the civilian providers each year from 2000 to 2006 was obtained from the manufacturer Sanofi-Pasteur. Previously conducted telephone interviews with healthcare providers have indicated little or no wastage of YF vaccine ... All 2941 authorized providers who provide an email address in the registry were surveyed by email to determine the total number of YF vaccine doses administered in 2006 and the date of birth (or age) and sex of each vaccinee. Overall, 1066 clinics responded to the survey, accounting for 95,828 doses (48%) of the approximately 200,000 doses administered to the civilian population in 2006. However, only 77,137 of these had age of vaccinee reported and 76,903 had sex of vaccinee reported, accounting for about 39% of the total number of doses distributed. The number of persons who received YF vaccine by age group and sex per year in the U.S. was estimated by multiplying the estimated total doses distributed each year by the proportion of vaccine recipients in each age and sex groups as determined from this survey [12].

Lindsey comments on the problems with VAERS as a passive reporting system:

Because VAERS is a passive surveillance system, adverse events are likely underreported. ...VAERS reports are also subject to coding errors. Because reports can be filed by a number of different sources, including vaccinees and their family members, the accuracy and completeness of the information provided in VAERS reports is variable. Most of the adverse events reported following YF vaccination (71%) occurred following receipt of multiple vaccines [12].

Because of the uncertainties in numerator and denominator due to combining individuals who received

yellow fever and other vaccines, we do not report Lindsey's detailed estimates here. Lindsey estimated the total number of doses of YF vaccine administered 2000-2006 as 1,534,170, and we estimate the reporting rate of a serious adverse event after yellow fever vaccination alone being administered as 15.6 (95% CI: 10.0 to 23.3) serious adverse events per million doses, and the reporting rate of YEL-AND as 7.82/million doses and YEL-AVD as 3.91/million doses.

Souayah (2007) [30] and Vellozzi (2006) [16] searched the database for individuals with specific illnesses. Souayah (2007) [30] looked for cases of Guillain-Barré Syndrome in only one year (2004) and identified 3 cases, each of whom received yellow fever vaccine and other vaccines, and no case data were provided. Vellozzi (2006) [16] searched for cases where corticosteroids were used as a treatment for YEL-AVD cases, and for 1996 to 2004 identified 11 cases and reviewed their medical records for clinical and laboratory data.

#### Databases which Provided Estimates of Serious Adverse Events But did Not Contribute to this Review

Five pharmacovigilance databases did not contribute data to this review, three because they did not provide denominators [31-33], and two because insufficient evidence was provided to attribute the events to yellow fever vaccination [34, 35].

**Bentancourt (2008) [33]** presented a brief report of the National Pharmacovigilance database of Brazil for January-May 2008 (most cases were from the low-risk Province of Corrientes). There was no assessment of whether surveillance is passive or active, or the quality of the data collection and assessment. No detailed definitions and no denominator data are provided. There were 153 reports of YF vaccine related events, of which 25 were vaccine related (assessed as 19 mild and 6 serious), 103 programme errors and 16 events not related to yellow fever vaccine.

**Health Canada** summarises reports sent to the VACART system from physicians (which are then reported to the regional Medical Officer of Health, who reports them to the provincial authorities, who then report them to the Division of Immunization at Health Canada), and also receives reports from manufacturers. The system is described as working on a "passive voluntary basis."

The reporting form consists of 25 predetermined adverse events of public health interest (VACART), which were originally developed mainly for the pediatric community. There also is a section for supplementary information. The latter is used to code additional adverse events using a reaction term thesaurus developed by the WHO (WHOART).

A report in 2002 summarised reports received between 1987 and 2000 [31]. There were 67 cases in which yellow fever vaccine alone was given, and 92 cases in which other vaccines were given. The reports of side effects were presented only for this entire set of 159 cases: 42 cases of allergic reaction, 38 fever (degree not stated), 29 severe pain/swelling, 15 rash; 13 arthralgia, 13 lymphadenopathy, 9

local reaction/swelling, 9 vomiting and/or diarrhea, 8 local abscess formation, 5 paralysis/paresthesia/tingling/hallucinations/screaming, 3 convulsions, 2 anaphylaxis, 1 Guillain-Barré syndrome, and 1 thrombocytopenia. There was no assessment of the quality and accuracy of the reports. The side effects for the 67 cases in which yellow fever alone was given are compiled with those where other vaccines were also given and no denominators were provided so we did not compute any rates.

**CDCP (2002) [32]** noted 117 reports of YF adverse events to the US database VAERS from June 20, 2001 to August 31, 2002, and 104 reports during a comparable period in 2000 to 2001. Case reports related to 6 persons with serious adverse events due to yellow fever vaccine consistent with YEL-AND neurological syndrome (4 cases) and YEL-AVD viscerotropic syndrome (2 cases).

**Fernandes (2005) [34]** studied notifications of all "vaccine adverse events" to any vaccine in the city of Juiz de Fora in Brazil. Passive surveillance consisted of notifications of events between January 1999 and December 2001 to the Brazilian National Immunisation program (SINAN). Although the totals of vaccine doses administered were recorded, they are not stated in the article. There was no assessment of the method of measurement of adverse events, and no assessment of data quality. There were 270 "vaccine adverse events" involving all vaccines, and 52 involving yellow fever vaccine, but no statement how many involved only yellow fever vaccine, and the descriptions of "adverse events" are listed only for the 270 events that involved all the vaccines. These "adverse events" included 113 local events (abscess, pain at the injection site, lymphadenopathy or ulcer) and 157 systemic events (including 110 fevers, 30 hypotonic/hyporesponsive episodes, 21 cases of hypersensitivity, 16 of persistent crying, 13 febrile convulsions, 11 cases of arthralgia, 7 cases of parotitis, 6 afebrile convulsions, and 5 cases of paresthesiae). There was no statement of any investigations of the cases of febrile convulsions. It was not stated which other vaccines had been administered with yellow fever vaccine. Fernandes computed a rate of 11.5 events/100,000 doses and a national rate of 0.6/100,000 for 1999-2001.

**Fernandes (2007) [35]** studied neurological adverse events following immunization (AEFI) "temporally associated" with yellow fever mass vaccination campaigns in the city of Juiz de Fora, Brazil, between 1999 and 2005. Passive surveillance consisted of notifications of events to the Brazilian National Immunisation programme from vaccination teams and health care workers on standardized forms. There was no assessment of data quality. Fifty-five adverse events "Attributed to yellow fever vaccine" were notified; and in 49 of these, yellow fever vaccine was the only vaccine administered. The most frequent events reported were 44 cases of fever, 39 of vomiting, 21 of headache, 10 of myalgia, 9 of meningismus, 9 of arthralgia, and 2 of jaundice. A total of 499,714 doses of YFV were administered between 1999 and 2005. Fernandes noted the problems of passive surveillance systems as:

- (i) both under-notification and over-notification,
- (ii) problems inherent to completion of the notification form and data

sources, (iii) poorly defined cases and (iv) inaccurate estimation of denominators [35].

No investigations were reported to verify the diagnosis of a vaccine reaction or differential diagnoses such as malaria or bacterial meningitis. Fernandes estimated the adverse rate as 11 events/100,000 doses. None of the events could have been assessed as severe except possibly the 9 cases of meningismus, for which no diagnostic tests are reported. Fernandes focused on “neurological adverse events” and there are no cases that could be categorically defined as YEL-AND [35].

## DISCUSSION

Reporting rates for serious adverse events following yellow fever vaccination are low. Differences in reporting rates may be due to differences in definitions, surveillance system organisation, methods of reporting cases, administration of YFV with other vaccines, incomplete information about denominators, time intervals for reporting events, the degree of passive reporting, access to diagnostic resources, and differences in time periods of reporting

**Definitions:** The definitions used to classify cases in the studies of the US VAERS by **Khromava (2005) [25]** and **Lindsey (2008) [12]** were very similar. Serious adverse events were assessed as resulting in death, life threatening illness, inpatient hospitalisation, prolongation of existing hospitalisation, or persistent or significant disability, with Khromava (2005) [25] adding “or other medically important condition.” **Martin (2001) [24]** provided a more detailed classification system. Adverse vaccine events were classified as neurologic (Guillain-Barré syndrome, new onset seizures, encephalitis, myelitis, altered mental status, focal cranial or peripheral neurologic deficits, paresthesias, vertigo, headaches [headaches alone were not sufficient for a neurologic diagnosis]), multisystemic (myalgias, arthralgias, rhabdomyolysis, elevated transaminases, respiratory distress, nausea, vomiting, diarrhea, nephropathy, disseminated intravascular coagulation, +/- fever), neurologic/systemic uncomplicated (rapid clinical recovery in < 72 hours), nonspecific events without other focal finding, hypersensitivity, local reaction, or unrelated to vaccine. Systemic adverse events were defined as neurologic or multisystemic.

The studies of the Brazil and Swiss databases used the WHO criteria. **Martins (2010) [21]** classified cases using the “CDC/WHO criteria” without further details other than to say they were classified as confirmed, probable or suspect, and without references to WHO publications. **Schumacher (2010) [22]** subdivided reactions by “organ system” as neurological (e.g. headache, convulsion), allergic (e.g. generalized urticaria, anaphylactic reactions), general systemic (e.g. fever, flu like symptoms), and local reactions (e.g. redness, swelling or pain at the injection site). Schumacher and his two co-authors analysed the data for all vaccines, and attributed the reported AEFIs to the vaccine which most likely caused the event, using the WHO classification for causal link (unclassifiable, unrelated, unlikely, possible, probable, or very likely/certain) and for severity: non-serious (mild severity), non-serious (moderate severity), and serious (severe). The definition of severe was:

“any untoward medical occurrence that results in death, hospitalization or prolongation of hospitalization, persistent or significant disability/incapacity, or is life threatening.” The WHO website used was referenced.

The classifications for the Australian and UK databases were broader than those for the other databases.

For the Australian ADRAC database **Lawrence (2004) [19]** classified cases as ‘systemic’ or ‘other’ adverse event and the ‘systemic events’ were then classified as neurological or multi-systemic. The definition of neurological events was wider than other databases (new onset seizures, encephalitis, myelitis, altered mental status, focal cranial or peripheral neurological deficits, paresthesia, vertigo, +/- headache) as was also the definition of multi-systemic events (myalgia, arthralgia, impaired hepatic function, respiratory distress, nausea, vomiting, impaired renal function, +/- fever). **Monath (2005) [23]** used broader definitions of adverse events than for most other databases: neurologic adverse events were defined as new onset seizures, encephalitis, myelitis, altered mental status, focal cranial or peripheral neurological deficits, Guillain-Barré syndrome, paresthesiae, vertigo, or headaches, and multisystemic events were defined as myalgias, arthralgias, rhabdomyolysis, elevated transaminases, respiratory distress, nausea, vomiting, diarrhea, nephropathy, disseminated intravascular coagulation, and fever. Headache alone did not qualify as an adverse neurologic event. The “serious adverse events” are not further classified into neurologic, multisystemic or “other serious adverse events.”

**Methods of reporting cases:** The reporting, training, and assessment systems are unique to each country. Although several countries reported laboratory testing could be used, in no study were the detailed laboratory tests reported that could conclusively identify cases as due to yellow fever vaccine (e.g. vaccine amplicon identification).

**Administration of other vaccines with yellow fever vaccine:** Databases often did not provide a detailed assessment of the cases in which only yellow fever vaccine was involved. They also often used overlapping classifications for “seriousness” and then the specific yellow fever vaccine YEL-AND and YEL-AVD events without clarifying the overlap.

**Lawrence (2004) [19]** noted 42 reports of adverse events for patients who received yellow fever vaccine and assessed 26 cases as “systemic,” 9 as “serious systemic,” none as “severe neurological disease,” and 1 as a fatal case of YEL-AVD. Fifteen of the reports involved only yellow fever vaccine, these reports are not further described, and only the one case of YEL-AVD can be definitely ascribed to this group. **Schumacher (2010) [22]** attributed events to the vaccine most likely to have caused the events, and if one vaccine could not be the preferred cause then equally to all vaccines involved, and did not report the proportion of cases in which yellow fever vaccine was administered with other vaccines. **Monath (2005) [23]** reported “serious adverse events” and did not further classify them into neurologic, multisystemic or “other serious adverse events.”

For the US VAERS database **Martin (2001) [24]** identified 35 systemic adverse events involving yellow fever vaccine, and 16 in which only yellow fever vaccine had been

given but reported rates for all 35 cases. **Khromava (2005) [25]** reported 465 civilian events involving yellow fever vaccine, with 430 non-serious, 7 YEL-AVD and 8 YEL-AND cases. In 190 reports (26%) yellow fever vaccine was administered alone, in 50% with typhoid or Hepatitis A vaccine or both, and in 24% the other vaccine was not specified. Because YEL-AVD and YEL-AND are unique to yellow fever we attributed them to the effects of yellow fever vaccine. **Lindsey (2008) [12]** similarly reported 660 cases in which yellow fever was given either alone or with other vaccines and there were 12 YEL-AND, 6 YEL-AVD and 28 cases of anaphylaxis. For the 190 cases in which only 17D was given, there were 24 serious adverse events: 7 life-threatening illnesses, 21 hospitalisations, 1 prolongation of a hospitalisation and 1 death. We attributed the 12 YEL-AND and 6 YEL-AND cases to this group, but the overlapping classifications are not clarified by Lindsey.

**Denominators: Lawrence (2004) [19]** computed the total number of 210,656 doses for the period 1993-2002 by extrapolation from Sanofi-Pasteur sales for 1999-2002, and extrapolated the age distribution of vaccinees for 1992-2002 from a 15% sample of vaccine clinics for 1999-2002. **Martin (2001) [24]** estimated age distribution of travellers from the GeoSentinel clinics receiving vaccine in 1998 and assumed these applied to the entire study (1990 to 1998) and was generalizable to the entire United States.

**Time intervals for reporting adverse events:** The definition of the time interval varied during which serious adverse events were reported. The usual time interval for accepting reports of serious adverse events is 30 days, but **Lawrence's [19, 20]** studies of the Australian ADRAC database recorded that serious adverse events reports were accepted up to two weeks after vaccination, while **Lindsey's [12]** study of the US VAERS database reported that serious adverse events incidents were included up to 60 days after vaccination.

**Degree of passive reporting:** The degree of passive reporting varied. The Swiss governmental database places a legal requirement on physicians to report serious adverse events [22] whereas in other countries the reporting of events tends to be passive, waiting for the vaccinees to report an adverse event then checking data with various degrees of active follow-up. There is an absence of a uniform method of reporting and then verifying adverse events data including symptom data, other vaccines administered, past medical history and laboratory data. Most databases have difficulty estimating adverse events in military personnel because military organisations may stockpile vaccine doses and may not wish to advertise the amount of wastage.

**Access to diagnostic resources:** The US VAERS and the Brazilian databases made explicit mention of access to diagnostic resources that could make definitive diagnoses of yellow fever vaccine in tissues, but publications about the pharmacovigilance data bases did not report the results for any individual case.

**Differences in time periods:** The reports span the period from 1990 to 2009, and surveillance systems and diagnostic technology have changed during these two decades.

## CONCLUSIONS

The 10 databases contributed approximately 107,600,000 patients to this review (allowing for overlapping time periods for the studies of the US VAERS database) and are very heavily weighted (94%) by the Brazilian database. The estimates of serious adverse events form three groups. 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 provide an estimate of 3.6/cases per million YEL-AND in one analysis and 7.8 in another, and 3.1 YEL-AVD in one analysis and 3.9 in another. The estimates for the UK used only the inclusive term of "serious adverse events" not further classified into YEL-And or YEL-AND and reported 34 "serious adverse events." The Swiss database used the term "serious adverse events" and reported 7 such events (including 4 "neurologic reactions") for a reporting rate of 25 "serious adverse events"/million doses.

The causes for differences in reporting rates and the level of the rates themselves listed in the discussion section can be grouped as several potential forms of bias: surveillance system bias (variations in the definitions used, the organisation, financing and training required to follow up all vaccinees for the period after YF vaccination); "misdiagnosis bias" (serious yellow fever vaccine reactions are misattributed as the individual also received other vaccines); detection bias; reporting bias; and "time and technology bias" (wealthier countries have more doctors, more resources and more access to publications, and more recent cases may be more likely to be reported accurately).

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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 GACVS 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 (RT/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 (RT/WS/DL); Statistical analyses and text (TW); writing the Interim and Final Reports for WHO (RET/DL).

## ABBREVIATIONS

|         |                                                 |
|---------|-------------------------------------------------|
| YF      | = Yellow fever                                  |
| YFV     | = Yellow fever vaccine                          |
| AEFI    | = Adverse event following immunization          |
| YEL-AND | = Yellow-fever associated neurologic disease    |
| YEL-AVD | = Yellow-fever associated viscerotropic disease |

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