



Public Health
England

Protecting and improving the nation's health

Guidance in the event of yellow fever vaccination in travellers with a contraindication or report of a yellow fever vaccine associated serious adverse event

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Introduction

Yellow fever (YF) is a live attenuated vaccine and has been associated with rare but serious adverse events (SAE) with the potential to cause significant morbidity and mortality. Further details regarding YF and the YF vaccine can be found in the Green Book (www.gov.uk/government/publications/yellow-fever-the-green-book-chapter-35).

YF vaccination is occasionally administered inadvertently to travellers with a contraindication. In England, Wales and Northern Ireland (EWNI), yellow fever vaccination centres (YVCs) are advised to report incidents and SAEs to NaTHNaC. There is no clear national or international consensus in the management of such cases.

Purpose and Scope

This document provides guidance and describes immediate actions recommended in the event of inadvertent yellow fever vaccination in a well or unwell traveller with a contraindication or the traveller experiencing a yellow fever vaccine associated SAE. This ensures timely reporting and appropriate prompt management of the case.

It is intended to be used by health professionals who regularly provide yellow fever advice and vaccination (eg health professionals working in travel clinics, GP surgeries, pharmacies, and those providing medical care to unwell adults who may have been exposed to vaccine (eg infectious diseases, accident and emergency, intensive care and liver units).

Contraindications to the Yellow Fever Vaccine

Please refer to the table (page 9) and Green Book for contraindications (www.gov.uk/government/publications/yellow-fever-the-green-book-chapter-35).

Serious Adverse Events

YF vaccination has been associated with serious adverse events (SAE) including YF associated viscerotropic disease (YEL AVD) and YF associated neurotropic disease (YEL AND).

YEL AVD occurs at a lower rate than YEL- AND at around 0.4 per 100 000 doses distributed worldwide in the US. It is similar to wild type YF disease and tends to include a systemic disease which can include hepatitis, renal dysfunction, and haematological disorders usually around 2-8 days after vaccination leading to multi-organ failure. It was first described in 2001, and over 100 confirmed and suspected cases have been reported worldwide (CDC Yellow book). Three cases have been reported in the United Kingdom until 2000, one in 1998 and 2 in 2000; all the UK cases survived (Thomas, 2016). Since then a further 2 cases have occurred in the UK in 2018 and in 2019. Unfortunately, both cases died. YEL-AVD has a mortality rate of over 60%.

YEL AND usually presents as meningitis or encephalitis but can present less commonly as Guillain–Barre Syndrome (GBS) or acute disseminated encephalomyelitis (ADEM). This is rare; reported rate in US 0.8 per 100 000 (Monath and Vasconcelos, 2015), with a higher reported rate in people aged ≥ 60 years of 2.2 per 100,000 doses (Lindsey et al., 2016).

Reporting and management of inadvertent YF vaccination or suspected yellow fever vaccine associated SAE

Healthcare workers who become aware of an inadvertent YF vaccination occurrence or suspected YEL-AVD or YEL-AND should liaise with their regional Infectious Disease team for clinical advice as soon as possible. If the patient is clinically unwell this should be done as an emergency to ensure urgent assessment and management.

In working hours (Monday to Friday 8.30am – 4.30pm) such incidents should be reported to the National Travel Health Network and Centre (NaTHNaC) via uclh.nursesatnathnac@nhs.net, ideally within 24 hours of the incident. NaTHNaC staff will support a coordinated response and access national expertise where necessary. Outside of these hours (working hours Monday to Friday 8.30am – 4.30pm) incidents should be reported to the on-call PHE duty doctor by phoning 020 8200 4400 and also to NaTHNaC via uclh.nursesatnathnac@nhs.net within 24 hours.

NaTHNaC will document all incidents in a database to aid future surveillance. Baseline data will be collected at the time of reporting by NaTHNaC, who will also follow up with the reporting clinician (as appropriate) at 60-days (see appendix 1 for risk assessment form indicating information to be collected). Please refer to page 6 for a flow chart of actions in this event, and page 7 for clearly defined roles and responsibilities.

YEL AVD and YEL AND can occur rapidly [YEL AVD mean and median; 5 days, YEL AND mean; 11 days, median; 14 days (Cottin, Niedrig and Domingo, 2013)(Lindsey *et al.*, 2016)] stressing the importance of immediate notification to allow time for urgent specialist Infectious Diseases assessment, including clinical, biochemical, virological monitoring and pre-emptive treatment where indicated.

Existing contraindications to yellow fever vaccine

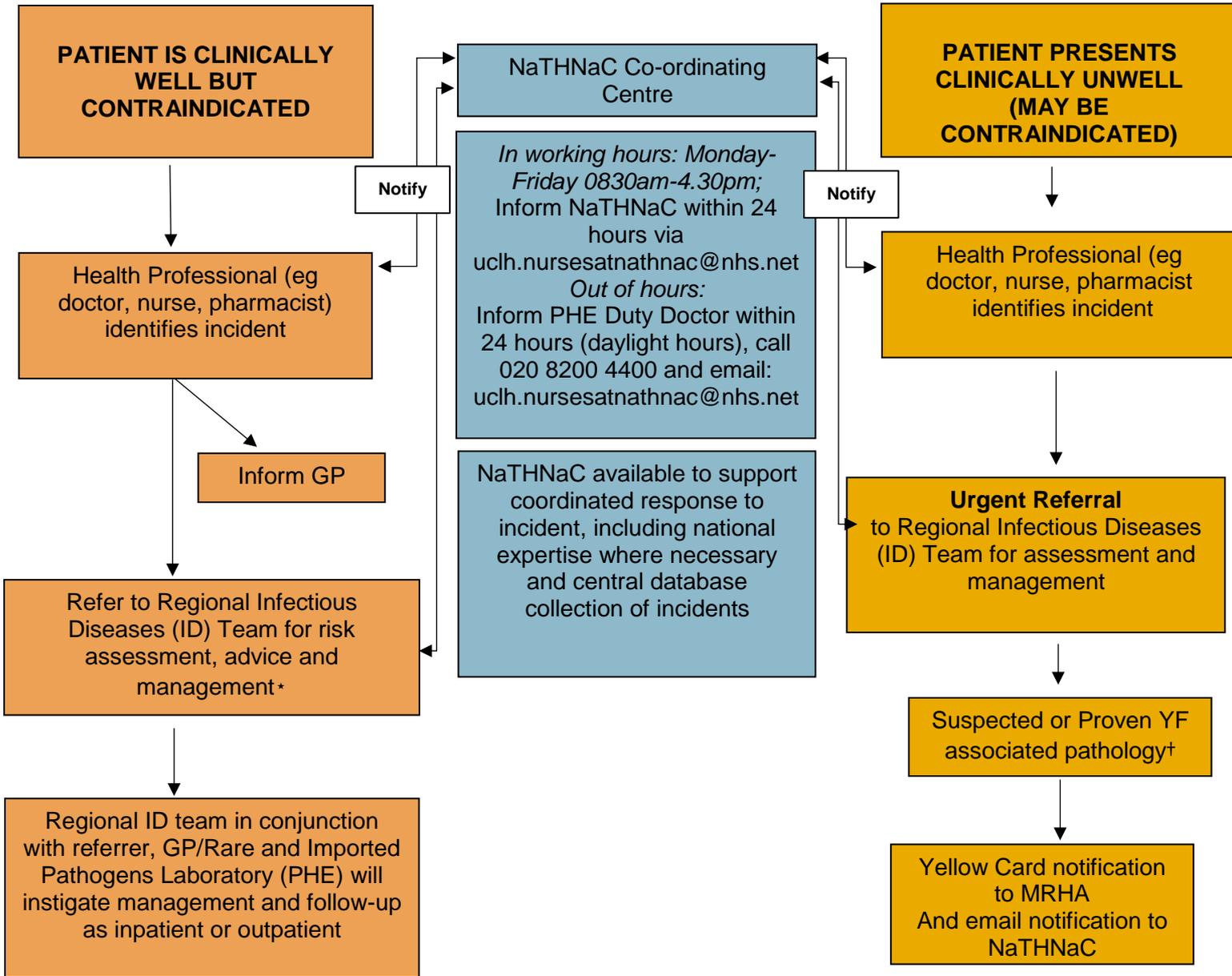
The vaccine should not be given to (please see the Green Book, chapter 35 for further information):

There are very few individuals who cannot receive yellow fever vaccine when it is recommended. Standardised checklists are available from NaTHNaC (<https://travelhealthpro.org.uk>) or Health Protection Scotland (www.travax.nhs.uk) and should be used before administering yellow fever vaccine. When there is doubt, appropriate advice should be sought from a travel health specialist.

The vaccine should not be given to:

- those aged under 6 months
- those who have had a confirmed anaphylactic reaction to a previous dose of yellow fever vaccine
- those who have had a confirmed anaphylactic reaction to any of the components of the vaccine, including egg
- those who have a history of thymus disorder or thymectomy for any reason including incidental thymectomy (eg during cardiac surgery)
- those with primary or acquired immunodeficiency due to a congenital condition or disease process including symptomatic HIV infection, and asymptomatic HIV infection when accompanied by evidence of impaired immune function
- those who are immunosuppressed as a result of treatment, including high dose systemic steroids, immunosuppressive biological therapy, radiotherapy or cytotoxic drugs
- those aged 60 years or older who are travelling to areas where yellow fever vaccine is generally not recommended by the WHO
- those who have a first-degree family history of YEL-AVD or YEL-AND following vaccination that was not related to a known medical risk factor

Flowchart of action required



* There is very little experience of using pre-emptive, experimental treatments to prevent YEL AVD; one case received rapid, pre-emptive treatment with an experimental antiviral agent at the Royal Free Hospital in 2018.

† In 2018, one patient with YF and 2 patients with YF AVD were treated at the Royal Free Hospital, London; further information and advice is available on request from the Royal Free (call 020 3758 2000 and ask for the Infectious Diseases doctor on-call).

Roles and responsibilities

Clinically Well		
	Responsibilities	Actions
Responsible clinician assessing vaccine recipient	Seek expertise for full risk assessment	<ol style="list-style-type: none"> 1. Refer to Regional Infectious Disease (ID) centre for risk assessment and management advice as soon as possible 2. Implement management advice in conjunction with other departments if indicated eg GP, Rare and imported pathogens laboratory (RIPL), hepatologist, neurologist 3. Notify NaTHNaC within 24 hours; out-of-hours and weekends contact PHE Duty Doctor (ensure NaTHNaC informed)
	Notification	
Regional ID centres	Risk assess vaccine recipient Formulate and implement management plan	<ol style="list-style-type: none"> 1. Risk assessment of vaccine recipient with regards to underlying co-morbidities 2. Formulate appropriate management plan in discussion with vaccine recipient 3. Carry out management plan in conjunction with relevant parties eg GP, RIPL 4. Ensure notification to NaTHNaC has occurred 5. National expertise can also be sought via NaTHNaC if required (see below)
	Update/notify NaTHNaC	
NaTHNaC	Coordinating Centre	<p>NaTHNaC is the coordinating centre for notification:</p> <ol style="list-style-type: none"> 1. Guide responsible clinician to regional ID centre for risk assessment and management if required† 2. Guide regional ID centre, if national expertise is required; for example, advise the regional ID centre that the Royal Free ID team has experience of managing cases and is happy to be contacted 3. Collection of case details, baseline clinical characteristics and 60 day follow up of clinical progress of case.
	Guide to national expertise	
	Case data collation	
Clinically Unwell		
Responsible clinician assessing vaccine recipient	Urgently refer for clinical assessment and management	<ol style="list-style-type: none"> 1. Urgently refer to Regional ID centre for risk assessment and management advice as soon as possible 2. Notify NaTHNaC within 24 hours; out-of-hours and weekends contact PHE Duty Doctor (ensure NaTHNaC informed)
	Notification	
	Assess and management patient	

<p>Regional ID centres</p>	<p>Notify NaTHNaC & MRHA</p>	<ol style="list-style-type: none"> 1. Assess and manage patient in conjunction with other parties eg RIPL, NaTHNaC, national experts with experience in these cases (see below) 2. Ensure notification to NaTHNaC has occurred 3. In suspected or proven YF associated pathology notify MRHA via yellow card system.
<p>NaTHNaC</p>	<p>Coordinating Centre</p> <hr/> <p>Guide to national expertise</p> <hr/> <p>Case data collation</p>	<p>NaTHNaC is coordinating centre for notification of inadvertent YF vaccination:</p> <ol style="list-style-type: none"> 1. Guide responsible clinician to regional ID centre for risk assessment and management if required 2. Guide regional ID centre, if national expertise is required; for example, advise the regional ID centre that the Royal Free ID team has experience of managing cases and is happy to be contacted 3. Collection of details of case, baseline clinical characteristics and 60 day follow up of clinical progress of case.

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Appendix 1:

Surveillance Form for Inadvertent YF vaccination to Contraindicated Groups or suspected SAE

RISK ASSESSMENT FORM

Date:	Time:	Location:
DOB:	Age	Gender
Date of YFV:	Lot no:	Exp date:
UKYFVC Number:	Date of departure:	
Reason for YF vaccine: Please include dates of travel and countries and areas intended to visit:		
Other reason for vaccination eg humanitarian worker, aircrew		
Contraindication (eg thymus disorder, HIV infection, previous transplant, immunosuppressant therapy):		
Details of this condition		
Names of drugs and doses of immunosuppressants including injectable: and duration		
Please describe incident:		
Please list all other comorbidities:		
Please list all other drugs and doses:		
Allergies and nature of allergy:		

Management Plan:

Please notify NaTHNaC via uclh.nursesatnathnac@nhs.net (Monday to Friday between 8.30am to 4.30pm) or the on-call PHE duty doctor (out of hours) .

Appendix 2: YF Vaccine Safety Data in General Population

International Definitions for Consistency

International definitions for adverse events from YF vaccine have been addressed by the Brighton Collaboration, conceived in 2001 to address the need for globally implemented and standardised case definitions, to enable consistency in data collection, aggregation and comparison to inform vaccine safety (Kohl *et al.*, 2005).

They have described case definitions to aid in the diagnosis of anaphylaxis (Rüggeberg *et al.*, 2007), YEL-AVD (Kohl *et al.*, 2005). And YEL- AND; with definitions for encephalitis, ADEM, myelitis (Sejvar *et al.*, 2007), aseptic meningitis (Tapiainen *et al.*, 2007), Guillain Barre Syndrome and Fisher syndrome (Sejvar *et al.*, 2011) that may be associated with YF vaccine.

The Brighton Collaboration also described virological based definitions classified as suspected, probable or confirmed based on laboratory confirmation of YF vaccine virus detection.

Vaccine Safety Data in General Population

Two reviews of vaccine safety have been done in the general population.

1. A Sanofi Pasteur Review of Stamaril Vaccinations in 2013 from Pharmacovigilance Data (Cottin, Niedrig and Domingo, 2013)

A 17-year review of 276 million doses distributed worldwide, 16.2 million in non-endemic countries, showed 95% of reported events concerned travellers from Europe, Australia and New Zealand (not distributed in North America) and 2% from endemic countries. Of 1460 medically confirmed reports, 805 were serious (potentially clinically compatible with YEL AVD, YEL AND and/ or hypersensitivity). Almost all (95%) reported events concerned travellers from Europe, Australia and New Zealand (Stamaril is not distributed in North America) with only 2% of cases reported from endemic countries in South America, mainly Brazil, Mexico and Argentina.

2. Safety Data from the US Vaccine Adverse Event Reporting System Regarding YF-VAX Vaccinations (Lindsey *et al.*, 2016a)

A review of adverse events from the US vaccine adverse event reporting system (VAERS) of the YF-VAX (Sanofi Pasteur) from 2007-13 identified 84 serious events

(defined as one of the following outcomes: death, life-threatening illness, hospitalization, prolongation of an existing hospitalization, permanent disability). Serious adverse events (SAE) occurred a median of 4 days after administration of the vaccine (range 0-60 days), 67% occurred within one week. There were 5 deaths including 2 cases of YEL AVD, one case of stroke, cardiac arrest and drug overdose with a reported rate 0.2 per 100 000 doses distributed calculated by the number of doses provided by the manufacturer.

A summary of rates of AE and SAE is shown in Table 1.

Table 1: Summary of adverse and serious adverse events in adults from the Sanofi Pasteur Review of 17D Stamaril Vaccination 2013 and the US Vaccine Adverse Event Reporting System of YF-VAX

Study	Stamaril Data Rates per 100 000 (Cottin, Niedrig and Domingo, 2013)	VAERS US Data Rates per 100 000 (Lindsey <i>et al.</i> , 2016b)
Adverse Events (AE)		
Overall AE	0.5	Not applicable (NA)
AE in travellers	9.2	NA
Overall AE in adults > 60y	0.05	NA
AE in adult travellers >60y	0.95	NA
Serious Adverse Events (SAE)		
Overall SAE	0.3	3.8*
SAE in travellers	5.1	NA
SAE in adults >60y	0.04	6.5 (60-69y) * 10.3 (≥ 70y) *
SAE in adult travellers >60y	0.7	NA
YEL AVD	0.004	0.3*
YEL AVD in travellers	0.07	NA
YEL AND	0.008	0.8*
YEL AND in travellers	0.15	NA

*This data is from US Vaccine Adverse Event Reporting System (VAERS) which is a non-endemic setting, therefore all vaccinees are travellers

Serious Adverse Reactions

1. Anaphylaxis

A table comparing of the total number and rates per 100 000 doses distributed of anaphylaxis adverse reactions as defined by the Brighton Collaboration definition (Rüggeberg *et al.*, 2007) is shown in table 2.

Table 2: Number of cases meeting Brighton Collaboration or CDC YF Working Group Case Definition for Anaphylaxis

Anaphylaxis events	Stamaril Data 2013 Reported cases per 100 000 doses	VAERS Data 2016 Reported cases per 100 000 doses
		Total cases = 33
Overall	0.01	1.4
European countries only	0.2	Not reported in data
In ages ≤ 18 years	Not reported in data	2.7

In the Stamaril review, 12 of 33 cases of anaphylaxis (all from Europe or Australia) were anaphylactic shock affecting adults and children. Mean age for all 33 reports was 26 years (range 4-59 years). Seven patients received concomitant vaccines. Twenty-three patients fully recovered, the status for the remaining 10 (all adults) is unknown. Food allergy or hypersensitivity to antibiotics was documented in 5 cases, including 2 patients with an allergy to eggs which is contraindicated for Stamaril immunisation. In 8 case reports 1-3 other vaccines were co-administered.

The VAERS review found mean age of 23 years (range 2-63 years), with the highest rate amongst those ≤ 18 years. Nineteen of thirty events occurred in males.

Anaphylaxis resulted in 3 hospitalisations and 27 additional emergency room visits. For the 26 anaphylactic reactions where the dose number was known, all occurred after primary vaccination. Co-administration with at least one other vaccine was described in 15 (50%) of the 30 event reports. Ten (33%) of the 30 anaphylaxis reports indicated some history of allergies. No reports indicated allergies to eggs or gelatin, but one report mentioned that the patient had a chicken allergy.

2. YEL AVD

YEL AVD cases are shown in table 3 including those that meet the Brighton and CDC YF Working Group (CDCYFWG) definitions.

Table 3; Number of cases meeting Brighton Collaboration or CDC YF Working Group Case Definition for YEL AVD

Definitions	Stamaril Data 2013	VAERS Data 2016
		Total cases = 12

	CDC YFWG	Brighton	CDC YFWG	Brighton
Definite	2	2	4*	6
Probable	3	3	0	0
Suspect	7	2	0	0
Insufficient data	0	5	0	0

*Remaining 2 cases not categorised

As shown in table 3, 12 cases of YEL AVD were reported after vaccination with Stamaril (Cottin, Niedrig and Domingo, 2013). Mean time of onset was 5 days (range 2-10d) (see table 5 for average incubation period for YEL AVD and YEL AND). Ten patients recovered and 2 died, one of whom had undergone a thymectomy for a benign tumour. Interestingly one case of 12 had a contraindication (benign thymoma with thymectomy). (Refer to appendix 4 for summary of all reported YEL AVD cases after vaccination with Stamaril from 1993-2010 (Cottin, Niedrig and Domingo, 2013)).

In the US VAERS data (Lindsey et al., 2016a) 6 cases met the YEL AVD Brighton Collaboration case definition. All occurred in males ≥ 70 years. Median time of onset from YF vaccination was 5 days (range 3-18). 2 patients died 14 and 20 days after vaccination. One of the cases met criteria for probable causal association with YF virus recovered from tissues, others had insufficient lab data. When case definition for YFWG was used, 4 cases met the YEL AVD criteria at a rate of 0.2 per 100 000 (Staples et al., 2010).

3. YEL AND

YEL AND cases are shown in table 4 including those that meet the Brighton and CDC YFWG definitions.

Table 4: Number of cases meeting Brighton Collaboration or CDC YF Working Group Case Definition for YEL AND

Definitions	Stamaril Data 2013		VAERS Data 2016	
	Total = 24		Total = 68 neurologic conditions	
	CDC YFWG	Brighton	CDCYFWG	Brighton
Definite	4	Not reported	13	17
Probable	6	Not reported	NA	NA

Suspect	14	Not reported		
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Of 24 cases from the Sanofi Pasteur pharmacovigilance data (Cottin, Niedrig and Domingo, 2013), 15 patients recovered and one patient died (8 lost to follow up). The death was from the only non-European case (Thai patient) with unrecognised HIV infection. Mean time to onset was 11 days (range 1-20). One case had testicular adenocarcinoma, one cellular immunodepression and one case had thymoma diagnosed and surgically removed during follow up investigations (appendix 5 for a list of all cases of YEL AND from 1993-2010 (Cottin, Niedrig and Domingo, 2013)).

From the US VAERS data (Lindsey et al., 2016a) of YEL AND cases, 17 events included GBS (n=7), aseptic meningitis (n=6), encephalitis (n=2), myelitis (n=2), and ADEM (n=1). Overall 12 cases (71%) occurred in males, median age 61 years. Median time of onset from vaccination was 14 days (range 3-60). 9 of the 17 cases had laboratory evidence of YF virus RNA or IgM antibodies in CSF.

Additionally, there were 51 reports of neurologic conditions that did not meet the Brighton case definitions including peripheral nerve disorder (n=20), encephalitis or altered mental state (n=13), seizure (n=7), cranial nerve palsies (n=4), movement disorders (n=4), meningitis (n=2) and chronic demyelinating polyneuropathy (n=1). Using the case definition previously used by YFWG (McMahon et al., 2007) 13 reports were classified as YEL AND (0.6 per 100 000 doses).

Incubation Period for YEL AVD and YEL AND

From the recent reviews of both the Stamaril vaccine (Cottin, Niedrig and Domingo, 2013) and the YF VAX (Lindsey et al., 2016b), mean and median time of onset from vaccine administration for YEL AVD and YEL AND are shown in table 5.

Table 5: Comparison of Average Incubation Period Observed for YEL AVD and YEL AND

Average	Study	YEL AVD (days)	YEL AND (days)
Mean	(Cottin, Niedrig and Domingo, 2013)	5 (range 2-10)	11 (range 1-20)
Median	(Lindsey <i>et al.</i> , 2016b)	5 (range 3-18)	14 (range 2-60)

Appendix 3: Vaccine Safety Data in People with Contraindications

Patients on immunosuppressant medications

A systematic review of the safety of live vaccines (MMR, YF, herpes zoster, varicella zoster, oral typhoid and polio, rotavirus, BCG, smallpox) in patients with immunosuppressive medication due to immune mediated inflammatory diseases (IMID), solid organ transplant (SOT), and patients < 2 years after bone marrow transplant (BMT), showed 233 patients with IMID received YF vaccine, 20 with SOT, and none with BMT. One participant with IMID developed an infection with the vaccine strain out of 233 vaccinated doses, none out of 20 SOT vaccine doses developed infection. The affected patient was a 49-year-old female with rheumatoid arthritis and systemic lupus erythematosus who started methotrexate and dexamethasone 4 days after YF vaccine was administered and developed YEL AVD and died. She was vaccinated as part of a mass campaign in Peru during which one particular vaccine lot was found to be associated with 20 times risk of YEL AVD (among 42 742 vaccinated persons, 5 developed YEL AVD) (Croce *et al.*, 2017)(Whittembury *et al.*, 2009).

Cottin et al reported 19 cases of inadvertent administration of 276 million doses of the YF vaccine (from 1460 AE reports of which 805 were SAE) (excluding the Thai patient) from patients on immunosuppressant therapy including methotrexate, azathioprine, cyclosporine, steroids, or patients living with HIV-1 infection with low CD4 counts showing no reports of YEL AVD or YEL AND (Cottin, Niedrig and Domingo, 2013). The systematic review (Porudominsky and Gotuzzo, 2018) also showed no increased risk in patients on steroids, methotrexate, azathioprine, leflunomide, cyclophosphamide, and some TNF alpha drugs such as infliximab and adalimumab but the numbers were limited.

This review included a report from Brazil (Oliveira *et al.*, 2015) in 31 patients with rheumatic disease (13 on methotrexate, 9 on leflunomide, 3 on infliximab, 3 on rituximab) who received YF vaccine (presumed for the 2nd time) reported mild adverse effects in the first 30 days – only 4 patients reported any symptoms; one patient with ankylosing spondylitis on 3.2g of mesalazine per day and one patient with rheumatoid arthritis on 10mg prednisolone per day developed myalgia, one patient with systemic sclerosis on 1.2g of cyclophosphamide per month had fever and rhinorrhoea and the other patient with rheumatoid arthritis on 20mg methotrexate a week and 1.5 sulphasalazine per day had arthralgia.

A Swiss retrospective study of 92 patients on immunosuppressants given any live vaccine included 8 patients on biologics (4 had sufficient interval from cessation to

vaccination), found no significant difference between the immunosuppressed cohort compared to controls regarding number of local and systemic reactions for YF vaccine with comparable severity (Huber *et al.*, 2018). Most patients were taking corticosteroids, with the second commonest medication mesalazine, followed by methotrexate. All doses were included. The median dose of corticosteroid was equivalent to 7.5mg of prednisolone per day, thus may not be comparable to the YF contraindicated groups recommended by the UK guidelines.

In haemopoetic stem cell transplant patients there are only case reports, but no SAE reported in 3 cases (Porudominsky and Gotuzzo, 2018).

Thymus Disorders

YF vaccine is contraindicated in those with a thymus disorder that is associated with abnormal immune cell function, such as thymoma or myasthenia gravis. This includes those who have had a thymectomy for a thymus disorder. In the reports of viscerotropic disease, 4 out of 23 cases (17%) had a history of thymus disease with subsequent thymectomy (Marfin *et al.*, 2005). A mathematical modelling paper of 64 reported cases of suspected YEL AVD supplied by Tom Monath (CDC) included endemic cases from South America and cases from travellers to YF prone areas in South America and Africa (Seligman, 2014). This calculated odd ratios using estimates of prevalence in a risk group of vaccinated population who did not become ill, compared to those that did with an odds ratio of YEL AVD of 140,000.

Patients living with HIV

The YF vaccine appears safe in patients living with HIV with low viral load and CD4 > 200 cells/mm³ but there is insufficient data for patients with CD4 < 200cells/mm³ (Porudominsky and Gotuzzo, 2018)

Potential New Risk Factors

Previous reviews showed increase of YEL-AVD cases in women aged 19-34 (Seligman, 2011) but this is preliminary data and needs further evaluation (Porudominsky and Gotuzzo, 2018).

Appendix 4:

Summary of all Reported YEL AVD Cases after Vaccination with Stamaril 1993-2010 (Cottin, Niedrig and Domingo, 2013). See table here:



Summary of all
Reported YEL AVD C

Appendix 5:

Summary of all Reported YEL AND Cases after Vaccination with Stamaril 1993-2010 (Cottin, Niedrig and Domingo, 2013). See table here:



Summary of all
Reported YEL AND C