YELLOW FEVER VACCINE - REPORT OF THE COMMISSION ON HUMAN MEDICINE’S EXPERT WORKING GROUP ON BENEFIT-RISK AND RISK MINIMISATION MEASURES

Following two fatal adverse reactions to yellow fever vaccine in the UK in 2018 and 2019, the UK Commission on Human Medicines (CHM) established an Expert Working Group to advise on measures that should be taken to optimise the balance of benefits and risks of the vaccine.

The Expert Working Group’s Terms of Reference were:

- To advise on the balance of benefits and risks of yellow fever vaccines
- To advise on measures to minimise risks, and optimise benefit-risk balance to individual vaccinees, including any new precautions or restrictions on use
- To advise on any communications to health professionals and potential vaccinees
- To advise on measures to monitor impact/effectiveness of any additional risk minimisation
- To report its conclusions and recommendations to the Commission on Human Medicines

The Expert Working Group was chaired by Professor Sir Munir Pirmohamed, and its full membership is at Annex A.

To inform its deliberations, the Group considered a review of available evidence on the safety and effectiveness of yellow fever vaccines from the Medicines and Healthcare products Regulatory Agency (MHRA), an analysis of the quality of batches of vaccine implicated in the recent fatal events, and evidence submitted by the licence holder, Sanofi Pasteur. The Group also considered contributions from the National Travel Health Network and Centre (NaTHNaC) and Health Protection Scotland (HPS) on the governance, clinical practice and training of yellow fever vaccination centres (YFVCs) across the UK, as well as ongoing work from Public Health England on a protocol for the management of severe adverse reactions to YF vaccine.

The Group met on 10th May 2019, 25th July 2019, and 4th October 2019 to consider the evidence and issued a series of recommendations, as summarised in this report, that were endorsed by CHM on 10 October 2019.
SUMMARY OF EVIDENCE CONSIDERED

The published evidence considered by the Expert Working Group is listed at Annex B.

Yellow fever

Yellow fever is an acute viral haemorrhagic illness caused by infection with the mosquito-borne yellow fever flavivirus. The main urban vector is the Aedes aegypti mosquito, which is found throughout the tropics.

The presentation of yellow fever disease ranges in severity from a subclinical, non-specific viral illness to a sudden onset systemic disease including fever, jaundice, haemorrhage, and renal failure. Differences in yellow fever virus strains, as well as host immune factors that are not fully understood, are likely responsible for the range of clinical symptoms. Mortality can be as high as 50%.

Nowadays the disease occurs in the tropical regions of Africa and Central and South America. Recent epidemics of yellow fever in Brazil and sub-Saharan Africa have become major public health concerns, for resident populations as well as travellers.

Accurate data on the burden of yellow fever are difficult to obtain because of variable quality of disease surveillance and underreporting of the disease. Approximately 138,000 cases of yellow fever, including 78,000 deaths, occur annually, with the vast majority of reported cases and deaths (>90%) occurring in sub-Saharan Africa.

Mosquitoes capable of transmitting yellow fever virus exist in regions where the disease does not presently occur and in regions, such as Asia, where yellow fever has never occurred. However, there is no risk of transmission in the UK from imported cases since the mosquito vectors are not present in the UK.

Overview of yellow fever vaccines

Yellow fever vaccines have been available for around 80 years. The currently available yellow fever vaccines are live, attenuated preparations of the 17D strain of yellow fever virus. More than 600 million doses of 17D yellow fever vaccines have been used worldwide. In the UK Sanofi Pasteur is the only marketing authorisation holder for yellow fever vaccine (Stamaril; 17D-204 strain).

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3 Barrett, A. The re-emergence of yellow fever. Science 361 (6405), 847-848. https://doi.org/10.1126/science.aaq8225
UK Immunisation recommendations and practices

Vaccination is recommended for persons aged nine months or older who are travelling to or living in areas or countries with a risk of yellow fever transmission⁵, as well as laboratory workers handling infected material.

Under the International Health Regulations (IHR) 2005 and to limit the spread of yellow fever, some countries require evidence of immunisation against yellow fever as a condition of entry, in the form of an International Certificate of Vaccination or Prophylaxis (ICVP). As a single dose of yellow fever vaccine is expected to confer life-long immunity, since July 2016 the ICVP is valid for the duration of the life of the person vaccinated.

Current guidelines for the practice of travel medicine advise that the risk of travel-associated yellow fever disease, the country ICVP requirements, and the potential for serious adverse events following yellow fever vaccination are considered as part of the individual risk assessment undertaken during a consultation at a travel clinic.

Where a health professional advises that an individual should not be vaccinated on medical grounds (e.g. due to a contraindication) and an ICVP requirement exists, a medical letter of exemption can be provided, which should be taken into consideration by the port/border health authorities in the destination country.

Yellow fever centres governance

Aside from the ICVP requirements, the IHR 2005 mandate that yellow fever vaccine can only be administered at yellow fever vaccination centres (YFVCs) designated by the health administration for the territory in which it is situated. These conditions are designed to ensure that individuals seeking yellow fever vaccine prior to travelling abroad have access to a formally registered YFVC, are provided with appropriate travel advice, and to help assure the quality and the safety of the procedures and materials employed. Such centres have to be suitably trained and follow a specific code of practice. In the UK, expert advice on travellers’ yellow fever exposure risk, designation of centres and country ICVP requirements are available through the National Travel Health Network and Centre (NaTHNaC) (https://nathnacyellowfeverzone.org.uk/) and Health Protection Scotland (HPS) (www.Travax.nhs.uk).

Each YFVC has to nominate a Responsible Supervising Clinician (RSC), who implements the conditions of designation and code of practice. YFVCs are responsible under the Conditions of Designation, for the reporting and follow-up of all vaccine adverse events to the Medicines and Healthcare products regulatory Agency (MHRA), Sanofi Pasteur, and NaTHNaC and HPS. YFVCs are also required to submit an annual return of yellow fever vaccine use.

⁵ WHO - List of countries, territories and areas - Yellow fever vaccination requirements and recommendations; malaria situation; and other vaccination requirements https://www.who.int/ith/ith_country_list.pdf?ua=1
HPS and NaTHNaC follow up incidents where yellow fever vaccine was administered inadvertently (i.e. where there was an unknown or undisclosed medical contraindication to the vaccine), as well as provide clinical support and advice. They also undertake an investigation of the clinical incident, which is referred with urgency to its yellow fever Designation Panel who considers sanctions against the YFVC as appropriate. These might include immediate temporary suspension (e.g. in the case of the recent two fatal events in the UK) and consideration of training options for HCP involved in the incident.

**Effectiveness of yellow fever vaccines**

No formal efficacy trials were performed before the first introduction of 17D yellow fever vaccines into operational use in the 1930s. The effectiveness of yellow fever vaccines has since largely been inferred from the vaccines’ ability to elicit neutralising antibodies in humans and protection in non-human primates against lethal challenge with yellow fever virus as well, as population-based declines in natural yellow fever disease following mass immunisation (compared to continued spread of yellow fever in neighbouring, unvaccinated countries). Following a single dose, seroconversion rates are generally higher than 90%. Recent estimates of yellow fever disease burden, modelled from African serosurveillance and case data, indicate immunisation programs have prevented 450,000 cases (95%CI = 340,000–560,000) and 28,000 deaths (95%CI = 7,200–62,000) in 2013.

**Safety profile of yellow fever vaccines**

The most common adverse reactions (ADRs) to yellow fever vaccines are similar to those that can occur following most attenuated, live vaccines. These are typically injection site and localised reactions, fever, headache, asthenia, general malaise and myalgia, all of which are common within one week of vaccination and are generally mild and transient.

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As with any vaccine, serious allergic reactions and anaphylaxis can occur very rarely, with passive surveillance suggesting a risk between 1 and 10 per 1 million doses.\(^9,10,11,12\)

**Unique serious side effects of yellow fever vaccines**

Reports of serious neurological reactions with 17D vaccines were documented in the 1950s, mostly in children aged under 7 months when there was no lower age restriction on vaccination.\(^13\) This led to the current contraindication for use in children aged under 6 months, and precautions for use from 6 to 9 months of age.

A risk of acute, fatal multi-organ failure resembling wild-type yellow fever infection, subsequently termed yellow fever vaccine-associated viscerotropic adverse reactions (YEL-AVD), was first identified in 2001. Closer scrutiny of safety from 2001 also led to more detailed characterisation of serious neurological adverse reactions, which are now termed yellow fever vaccine-associated neurotropic disease (YEL-AND). YEL-AVD and YEL-AND can resemble the multi-organ failure and neurological effects that can follow wild yellow fever infection.

Cases of YEL-AVD and YEL-AND have so far been identified only in primary vaccinees. Most reported cases of YEL-AND have recovered (~2% mortality), but YEL-AVD has been associated with up to 50% mortality.\(^2\) Available evidence suggests the overall risk of both YEL-AND and YEL-AVD to be in the order of 1 case per 100,000 vaccinees, with a greater risk in certain sub-groups. The known risk factors (other than age under 9 months) for YEL-AND and YEL-AVD are similar; i.e. conditions that pose a risk of over-replication of yellow fever vaccine virus, notably immunosuppression and advancing age.

There is a greater risk of YEL-AVD in older age vaccinees, with at least a 4-fold increase in the reporting rate of YEL-AVD, and a 2-fold greater rate of YEL-AND, in those aged 60 years and over.\(^14,15\) However, unlike YEL-AVD for which the vast majority of reported cases fall into one or more of these risk groups or older people,

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\(^12\) Kelso, J et al. Anaphylaxis from yellow fever vaccine. Journal of Allergy and Clinical Immunology. Volume 103, Issue 4, April 1999, Pages 698-701. [https://doi.org/10.1016/S0091-6749(99)70245-9](https://doi.org/10.1016/S0091-6749(99)70245-9)


a greater proportion of reported cases of YEL-AND are in younger age groups and those without any obvious risk factors.

Thymus dysfunction, and history of thymectomy due to thymoma, are identified risk factors for YEL-AVD\textsuperscript{16}. Some studies have also suggested an increased risk for YEL-AVD associated with systemic lupus erythematosus and autoimmune disease\textsuperscript{17}.

Cases of YEL-AVD without obvious risk factors, including cases in otherwise young and healthy people have also been reported, and genetic factors are likely to influence individual susceptibility to serious ADRs to yellow fever vaccine, particularly those that can influence immune regulation. Indeed, aside from environmental aspects that will influence the apparent lower rates of YEL-AVD in endemic populations compared to travellers (e.g. pre-existing vaccination, previous exposure to yellow fever virus and cross-protection from exposure to other flaviviruses), the genetic characteristics of populations in African and South American countries may play a role in this. Indirect evidence also comes from the observation of two cases of YEL-AVD reported in siblings in Brazil\textsuperscript{18}. However, there is very little direct human evidence to determine what these specific genetic factors may be. In one study polymorphisms in the genes that encode for chemokine receptor CCR5, and its ligand RANTES led the authors to speculate that a defect in innate immunity may have been observed in one of the AVD cases studied\textsuperscript{19}. Other authors have reported an unexpected decrease in the levels of CXCR3 expression by CD4\textsuperscript{+} and CD8\textsuperscript{+} T cells, and also speculated that abnormalities in the innate immune response may have been a factor in another AVD case\textsuperscript{20}. Genetic factors will influence the nature of the inflammatory response to vaccination and the immunopathology of YEL-AVD. Other cases of YEL-AVD have reported a range of cytokine and chemokine responses\textsuperscript{21}, and have been described as a systemic inflammatory syndrome and ‘cytokine storm’, and a recent UK case presented with features of hemophagocytic lymphohistiocytosis (HLH).

**Previous safety reviews**

Following a review of the evidence by the UK Committee on Safety of Medicines (CSM) and its Sub-Committee on Pharmacovigilance (SCOP) in 2001, warnings and


a precaution about use in subjects aged 60 year or above were included in the Summary of Product Characteristics (SmPC).

Further review of case reports in 2005 suggested that a significant number of cases of YEL-AVD had a history of thymus disorder and, following a further CSM review, use in those a with a history of thymus dysfunction became an SmPC contraindication, and warnings on the risk of YEL-AND and YEL-AVD were expanded.

The product information was further strengthened following a European article 30 referral in 2005 and the SmPC for Stamaril was harmonised across the EU. This also led to an SmPC recommendation that the vaccine should only be given to the elderly (defined in the SmPC as from 60 years of age) if it is considered that there is a considerable and unavoidable risk of risk of acquiring yellow fever infection during travel, due to the risk of YEL-AVD.

In 2013, the WHO’s Strategic Advisory Group of Experts on Immunisation (SAGE) Working Group on yellow fever Vaccines updated their recommendations stating that the vaccine offers a life-long protection against yellow fever disease and a booster dose of yellow fever vaccine is not generally needed, revaccination being reserved only to specific risk groups (such as infants or HIV-infected patients) that could benefit from a second primary or booster dose. On people over 60 years of age SAGE noted that while the risk of YF-AVD is higher than in younger groups, the overall risk remains low and vaccination should be recommended based on a careful risk–benefit assessment comparing the risk of acquiring yellow fever disease versus the risk of a potential serious adverse event following immunisation. It also concluded that the vaccine should not be administered to severely immunocompromised subjects.

Overview of UK adverse reaction (ADR) reports

Between 1967 and April 2019, the MHRA received 691 spontaneous ADRs in total associated with yellow fever vaccine via the Yellow Card Scheme. Of these, 13 reports related to possible viscerotropic disease, of which 7 were fatal. A total of 50 cases of possible YEL-AND were reported over this time, none of which were fatal. The total number of suspected ADRs for yellow fever vaccine reported via the Yellow Card Scheme is currently less than 40 in the UK per year, following administration of approximately 140,000 doses of yellow fever vaccine per year.

Based on reports of possible YEL-AVD received between 2013 and 2018 (years for which vaccine exposure data was available), the UK reporting rate of YEL-AVD was estimated at 0.2 per 100,000 doses administered. The UK reporting rate of possible YEL-AND over this time was estimated at 1.8 to 5.9 per 100,000 doses administered.
Of the two recent UK fatal reports of YEL-AVD, one concerns a patient who had previously undergone a thymectomy, having developed a thymoma, and the second concerned a 67-year old male in whom there were no other known risk factors. Analysis by the official medicines control laboratory of samples from the batches implicated in the two recent fatal cases did not reveal unusual findings.

CONCLUSIONS AND RECOMMENDATIONS OF THE EXPERT WORKING GROUP (EWG)

The EWG agreed that wild-type yellow fever infection is serious with high mortality, and that the evidence on the ability of yellow fever vaccines to protect individual vaccinees appears robust. The EWG also agreed that, in the context of the current benefit-risk assessment and its terms of reference, the key benefit question is how to quantify the risk of exposure to yellow fever in any particular environment, and thereby the benefit of vaccination to an individual traveller based on their intended travel destination and activities. The EWG also agreed that YEL-AVD and YEL-AND are the key, life-threatening, albeit rare, risks affecting the risk-benefit balance in an individual.

Authorised indication for use of yellow fever vaccine and need for revaccination

The EWG advised that the balance of benefits and risks of yellow fever vaccine remains favourable for most travellers when used in accordance with the current authorised indications in the summary of product characteristics (SmPC). The EWG considered that use of the term ‘endemic area’ in the indication may not be helpful as endemcity is complex to ascertain in real time. This also does not include areas where there are no human cases because universal immunisation programs have conferred immunity to the local population but, because of the natural transmission cycle in non-human primates and mosquitoes, there is the potential of virus infected mosquitoes, and therefore transmission to unprotected persons. The EWG therefore recommended alternative wording should be used in the indication: “an area where there is a current or periodic risk of yellow fever transmission”

The EWG also recommended that, in line with WHO recommendations on yellow fever vaccination, the SmPC should specify that revaccination is not generally recommended, but may still be required in certain populations defined by the WHO and national guidance.
**Risk factors for YEL-AVD and YEL-AND**

**Persons aged 60 years and over**

The EWG advised that the balance of benefits and risks of yellow fever vaccine remains overall favourable in persons aged 60 years and over. However, due to the greater risk of YEL-AVD and YEL-AND, the benefit-risk balance may be unfavourable for destinations where there is no or minimal risk of acquiring yellow fever infection. The EWG therefore recommended that the current SmPC precaution that “the vaccine should only be given when it is considered that there is a significant and unavoidable risk of acquiring yellow fever infection” should be further clarified to inform individual risk assessments with the addition of “such as travel to an area where there is a current or periodic risk of yellow fever transmission”.

The EWG considered that while quantifying the absolute risk of yellow fever infection for an individual traveller is generally not possible on a real-time basis, countries and areas designated by WHO as where vaccination is ‘generally not’ recommended, or not recommended, should be considered as not representing a ‘significant and unavoidable risk’. Therefore, the benefit-risk of vaccination for persons aged 60 years and over visiting one of these areas would be considered unfavourable and so yellow fever vaccination should not be recommended. The EWG noted that a letter of exemption from vaccination is issued for a single trip and recommended that this could be considered as an option for those at minimal risk of exposure who may require official documentation due to their travel itinerary.

**Thymectomy**

The EWG considered that the thymus gland has a continuing function in adulthood in maintaining the diversity of T cells, that involution of the thymus gland with advancing age reduces the T cell repertoire and that thymectomy is likely to accelerate immunosenescence. Based on the limited evidence available at the present time the EWG agreed that an increased risk of serious adverse reactions in those with a history of incidental thymectomy at any age and for any reason cannot be excluded. The current contraindication in the SmPC should be further clarified to reflect thymectomy for any reason as a risk factor in itself: “History of thymus dysfunction (including myasthenia gravis, thymoma)” and “Thymectomy (for any reasons)”. The EWG advised that the recommendation should be also reflected in the Green Book.

The EWG agreed that the Green Book should also specify that those who underwent surgery for congenital heart disease should be considered at high risk of developing complications following vaccination because for this group, thymectomy is routinely performed during cardiothoracic surgery to enable better access to the heart and great vessels. Therefore, a precautionary approach should be used unless there is evidence that their thymus was not removed.
Autoimmune conditions

The current contraindications to yellow fever vaccine administration are immunosuppression and history of thymus dysfunction (including myasthenia gravis, thymoma, thymectomy). The EWG agreed that severely immunocompromised patients should not receive the vaccine, and after reviewing evidence from publications advised that there is insufficient evidence to add other autoimmune conditions to the list of contraindications at this time.

Immunomodulating biological products

The EWG agreed that balance of benefits and risks of yellow fever vaccine is likely to be unfavorable with concomitant use of most immunomodulating biological products and therefore this should be reflected as a contraindication.

The EWG recommended that the list of immunosuppressant therapies mentioned in the contraindications section of the product information is updated to include “other drugs with known immunosuppressive or immunomodulatory properties and current or recent radiation therapies targeting immune cells.”

The EWG also advised that the treatment regimen is evaluated during the individual risk assessment and in case of doubt, protocols should advise that the treating physician is contacted to confirm if the patients can receive the vaccine.

Genetic risk factors and family history of YEL-AVD and YEL-AND

The EWG considered evidence from Brazilian case reports in which two sets of siblings experienced YEL-AVD following yellow fever vaccination. Evidence from several publications suggesting that certain genetic polymorphisms, such as chemokine receptor CCR5/RANTES, may be a risk factor for YEL-AVD was also considered, as well as evidence of genetic risk factors from animal models.

The EWG agreed that, although there is currently insufficient evidence to determine what specific genetic risk factors pose an increased risk of serious adverse reactions, and that more research is needed to inform this, it was very likely that genetic susceptibility plays an important role. The EWG therefore recommended that the balance of benefits and risks is likely to be unfavourable in those who have a first-degree family history of YEL-AVD or YEL-AND which was not explained by immunosuppression or history of thymectomy/thymus dysfunction, and that such use should be a contraindication to vaccination.

Women of child-bearing potential

The EWG considered evidence from publications suggesting that reporting rates of YEL-AVD may be higher in women of child-bearing age. However, the EWG advised that this was based on a small number of case reports and because there was
insufficient evidence to confirm or refute this that the balance of benefits and risks in this group remains unchanged.

**Description of YEL-AVD and YEL-AND in Stamaril product information**

The EWG considered YEL-AVD and YEL-AND, the key, life-threatening risks associated with the vaccine, to be well defined in the product information. However, some of the early signs and symptoms of YEL-AVD and YEL-AND are the same as those commonly reported, non-serious adverse reactions following vaccination (e.g. fever, headache, and myalgia). Therefore, the EWG recommended that the product information wording should be carefully balanced to avoid causing unnecessary alarm to the vaccinee and consideration should be given to define a time-frame which distinguishes between the milder symptoms commonly experienced post-vaccination and the more severe symptoms of YEL-AVD and YEL-AND. The EWG agreed that additional information should be added to the product information to advise healthcare professionals to highlight the signs and symptoms to vaccinees and instruct them to seek medical attention as they may be suggestive of severe adverse reactions.

The EWG advised that it is important that travellers are reminded not only about symptoms of YEL-AVD and YEL-AND but also of the need to inform their HCPs about having received yellow fever vaccine when they seek medical attention after feeling unwell.

**Psychiatric adverse events**

Psychiatric events are not currently listed in the product information as a possible adverse reaction to yellow fever vaccine, either in isolation or as part of YEL-AND. The EWG considered that acute psychiatric symptoms can be a manifestation of encephalitis and advised that, based on evidence from spontaneous ADR reports, “change in behaviour” and “new onset of psychiatric symptoms” should be added to the product information as part of the YEL-AND description.

However, available evidence at the present time is insufficient to determine whether acute or chronic psychosis may be a specific adverse reaction to yellow fever vaccine. It was considered that acute psychosis could be part of the clinical manifestation of any neuroinflammatory or autoimmune event, but it is more difficult to determine if these symptoms may become chronic after the encephalitis has resolved.

The EWG agreed that it is plausible that encephalitis associated with anti-NMDAR antibodies is part of the YEL-AND spectrum of disease. However, the EWG advised that the available evidence is insufficient to determine if anti-NMDA encephalitis may be a risk of yellow fever vaccination and that further data from case studies and individual reports would be required.
Strategies to reduce the burden of adverse reactions to yellow fever vaccines

The EWG considered that there is need improve the risk-benefit balance of yellow fever vaccine by reducing the burden of adverse reactions where possible and specifically recommended improved communication to patients, standardisation of the checklist used by healthcare professionals to screen for contraindicated or high risk patients, and further standardisation of healthcare professional training. Further details on the recommended actions are provided below.

Information available to patients

The EWG considered the information that is provided to vaccinees on the possible risks of yellow fever vaccine, including the signs and symptoms of YEL-AVD and YEL-AND, to support early identification and rapid treatment referral for such events. The EWG advised that the authorised patient information leaflet (PIL) should serve this purpose but considered that its wording should be amended and further clarified.

Differences in clinical practice were reported, with only some healthcare professionals providing the authorised PIL to potential vaccinees as part of the travel consultation. The EWG recommended that the authorised PIL should be provided to each person receiving the vaccine. In addition, given that the early signs and symptoms of YEL-AVD and YEL-AND overlap with the most common, non-serious expected ADRs to yellow fever vaccine (e.g. fever and malaise), the EWG advised the wording should be carefully balanced to avoid causing alarm to vaccinees and that the recommended changes to the SmPC should be carefully reflected in the PIL.

Risk minimisation measures

The EWG recognised the important role of HPS and NaTHNaC in overseeing, in line with WHO requirements, a programme of registration and designation, training, standards and audit that is mandatory for all YFVCs.

The EWG recommended that due to the importance of screening travellers for contraindications to vaccination, and the determination of ‘significant and unavoidable risk’ of yellow fever infection in the assessment of whether or not an individual should receive yellow fever vaccine, there is a need for a standardised approach in the risk assessment process.

The EWG recommended that, for all travellers, the individual risk assessment and yellow fever vaccine administration should be carried out by a qualified and trained health care professional with experience in benefit risk evaluation of yellow fever vaccine. The group recommended that this requirement should be reflected in the product information, in guidance on travel health practice, and patient group directions (PGDs) concerning yellow fever vaccine.

The EWG considered that to ensure a standardised approach to individual risk assessment for yellow fever vaccination, the checklists used by both patients and
healthcare professionals should be formally implemented via the Stamaril statutory Risk Management Plan (RMP), with the objective of increasing compliance with indications, contraindications, warnings and precautions. The EWG noted that this approach would make the checklist a statutory requirement for the use of yellow fever vaccine in the UK. The EWG agreed on the need to develop a yellow fever risk assessment/screening tool that the healthcare professional completes with the patient during the travel health risk assessment.

The EWG also agreed on the need for the marketing authorisation holder to make proposals to evaluate the effectiveness of these risk minimisation measures using a standardised approach, involving both the checklist and the patient information leaflet.

YFVCs are already required to submit an annual return of yellow fever vaccine use to NaTHNaC, and the EWG proposed that centres should also report data on subjects that were refused the vaccine, with a brief explanation of the reason for refusal/ineligibility.

The EGW also considered it important to encourage not only the reporting of suspected adverse reactions but also of “near miss” events, defined as incidents or errors in which no personal injury occurred, but where a slight change in circumstances could have resulted in harm.

Training

The EWG considered that the initial training in yellow fever vaccination currently provided by HPS and NaTHNaC should be mandatory for all HCPs administering the vaccines and a refresher should be carried on a regular basis (e.g. every 2 years). The EWG recommended that a standardised mandatory assessment is carried out after the training.

Public Health England treatment guidance for severe adverse reactions to yellow fever vaccine

The EWG supported the initiative from Public Health England (PHE) to develop guidance on the treatment of severe adverse reactions to yellow fever vaccine by providing information to health care professionals of the treatment services that have expertise in this area and stating where patients should be referred for investigation and treatment.

Existing UK resources on yellow fever vaccine

The EWG recommended that HPS, MHRA, NaTHNaC, and PHE should work together to ensure harmonisation of information on contraindications and cautions for use of yellow fever vaccine across the authorised product information (SmPC and PIL), the Green Book and their respective organisational websites.
The EWG recommended that MHRA closely collaborate with HPS, NaTHNaC, and PHE on amending existing guidance (e.g. Green Book), risk minimisation material, and HCPs training to reflect the EWG’s recommendations.

**Perspective on the future research and development of Yellow fever vaccines.**

To further support research, the EWG considered that it is important to develop and validate a standardised neutralising antibody assay that can be used to measure the immune responses in vaccinees. This would enable future studies to define what level of antibody production correlates with protection and to compare immunogenicity data across different studies.

**Evaluation of vaccine safety and risk factors**

The EWG considered that a repository of tissue and blood samples from YEL-AVD and YEL-AND patients similar to the one existing in the United States could be useful as it could be used by researchers to further study yellow fever vaccine safety and risk factors for severe adverse events.

The EWG also noted that whilst it is difficult to study wild-type yellow fever infection, up to 50% of yellow fever vaccinees develop transient viraemia. This could offer an opportunity for drug discovery and development by undertaking proof of concept studies on experimental therapies.

The EWG recommended further research aiming at clarifying the role of the thymus and thymectomy and the associated increased risk of severe side effects to yellow fever vaccine. For this purpose a possible approach might be to use the Clinical Practice Research Datalink (CPRD) and to set up a case control or cohort study to further clarify the risk of YEL-AVD and YEL-AND observed in specific groups such as patients who had a thymectomy (or incidental thymectomy during cardiac surgery) or are immunosuppressed.

The EWG also supported developing further research on the role of immunosuppression as a risk factor for severe complications of yellow fever vaccine, and the definition of the most appropriate timing for a booster dose in cases of immunosuppressed individuals for whom the vaccine is not contraindicated.

**Upper limit for vaccine potency**

The EWG noted that there is no upper limit to the quantity of vaccine virus in each dose and that, whilst average doses range between 13,000 and 43,000 IU, individual batches have contained several hundred thousand or more IU per dose. Although there is no evidence of batch-specific risks of YEL-AVD and YEL-AND, no analyses have been published that correlate case reports with the IU per dose the EWG recommended that more consideration should be given in defining an upper limit for the potency of yellow fever vaccine.
Fractional dose vaccines

The EWG noted that fractional doses have been used in outbreak situations when there is a shortage of yellow fever vaccine, and that the WHO decision of using one-fifth of the dose in such situations is a decision based on empirical and practical considerations rather than existing evidence. However, studies are on-going, and the latest evidence indicates that fractional dosing can elicit an immune response, with a recent study reporting that seropositivity was maintained in 85% of 318 vaccinees 8 years after receiving the vaccine.22

The EWG considered that there is currently limited evidence to determine whether fractional doses are associated with a reduced risk of YEL-AVD and YEL-AND. The use of fractional dosing has mostly been in used in populations where yellow fever is endemic (and therefore the background risk is different for travellers due to existing immunity and cross-protection). The EWG noted that only one study on fractional dosing is being carried out in a non-endemic setting but results are not yet available. However, on the basis that the vaccine virus is likely to replicate rapidly and achieve a viral load in the host similar to a full dose, the EWG considered that a fractional dose may not necessarily lower the risk of serious adverse reactions.

Based on the existing evidence the EWG considered that fractional dosing does not constitute a suitable alternative to existing available vaccine for high risk travellers. The EWG recommends that further studies in non-endemic countries should be carried out to evaluate long term protection in this populations.

Inactivated and non-replicating vaccines

The EWG heard that inactivated yellow fever vaccines are in development but noted that these pose issues related to long term protection, manufacturability, and costs and are unlikely to be available in the near future. Nevertheless, the EWG considered that further development of inactivated and non-replicating vaccine should be encouraged, for example aimed at improving vaccine formulations. In addition, the EWG considered that studies should be carried out to explore the use of these 'non-live' vaccines in association with live attenuated vaccines as part of a vaccination strategy aimed at minimising the risk of YEL-AVD and YEL-AND. This could include primary administration with a non-replicating vaccine to elicit an initial immune response followed by a booster using an attenuated vaccine to confer long term protection.

Communication strategy

The EWG agreed on a communication strategy for the findings of this safety review. The proceedings of the EWG will be published in a summary assessment report and an MHRA Drug Safety Update article that will be disseminated to the health care professionals working in travel clinics. The MHRA will work in close collaboration with HPS and NaTHNaC to ensure that HCPs and travellers are informed of the conclusions of the EWG.
Annex A

YELLOW FEVER VACCINE EXPERT WORKING GROUP MEMBERSHIP

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ANNEX B

Published evidence considered by the Expert Working Group


7. A global strategy to Eliminate Yellow fever Epidemics (EYE) 2017 – 2026 https://apps.who.int/iris/bitstream/handle/10665/272408/9789241513661-eng.pdf?ua=1


15. WHO - List of countries, territories and areas - Yellow fever vaccination requirements and recommendations; malaria situation; and other vaccination requirements https://www.who.int/ith/ith_country_list.pdf?ua=1

16. WHO - Countries with risk of yellow fever transmission and countries requiring yellow fever vaccination https://www.who.int/ith/ith-yellow-fever-annex1.pdf?ua=1


18. A global strategy to Eliminate Yellow fever Epidemics (EYE) 2017 – 2026 https://apps.who.int/iris/bitstream/handle/10665/272408/9789241513661-eng.pdf?ua=1


20. Martins M et al. Innate immunity phenotypic features point toward simultaneous raise of activation and modulation events following 17DD live attenuated yellow fever first-time vaccination. Vaccine
29. WHO - Recommendations to Assure the Quality, Safety and Efficacy of Live Attenuated Yellow Fever Vaccines. Proposed replacement of: TRS 872, Annex 2 and Amendment to TRS 872.
37. https://reliefweb.int/sites/reliefweb.int/files/resources/OEW16-1521042019_0.pdf
46. Vasconcelos et al. Serious adverse events associated with yellow fever 17DD vaccine in Brazil: a report of two cases. The Lancet. Volume 358, Issue 9276, 14 July 2001, Pages 91-97. [https://doi.org/10.1016/S0140-6736(01)05326-0](https://doi.org/10.1016/S0140-6736(01)05326-0)


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