

# Safety and tolerability of yellow fever vaccines

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Yellow fever is a non-contagious, viral, multisystem syndrome, that causes an estimated 200 000 human infections annually, and has a high fatality rate. Yellow fever vaccination is one of the main methods of primary prevention. Although the yellow fever vaccine is largely considered to be safe, adverse events, which are sometimes life-threatening, can occur. This article explores the safety and tolerability of yellow fever vaccines.

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## Introduction

Yellow fever is a non-contagious, multisystem syndrome caused by a vector-borne arbovirus from the flavivirus genus of the Flaviviridae family.<sup>1</sup> The Flaviviridae family contains over 70 related, but distinct, viruses, of which some are known to cause haemorrhagic fever, or acute encephalitis.<sup>1</sup> In Africa, the main vectors of yellow fever are mosquitoes of the genus *Aedes*, subgenera *Stegomyia* and *Diceromyia*.<sup>2</sup>

The case definition for yellow fever is an illness in a patient of any age, residing in, or with a history of recent travel to, an endemic country, who presents with high fever, severe headache, neck and back pain, possibly accompanied by vomiting, abdominal pain, diarrhoea, haematemesis, bloody diarrhoea, jaundice and epistaxis.<sup>3</sup>

## Yellow fever: burden of disease

It is estimated by the World Health Organization (WHO) that about 200 000 cases of yellow fever occur in endemic areas (tropical Africa and South America), annually. However, only a small percentage of these cases are reported.<sup>1</sup> Globally, an estimated 30 000 deaths are attributable to yellow fever annually, with significant mortality among unvaccinated travellers to endemic areas.<sup>4</sup> In 2002, WHO reported that, of the 30 000 yellow fever-related deaths that occurred in countries where vaccination is part of the national immunisation schedule, 50% of deaths occurred in children under the age of five.<sup>5</sup> Despite an increase in overall vaccine coverage, epidemics have continued to occur, particularly between 1985-1995.<sup>6</sup>

## Yellow fever vaccine

There are two main methods of preventing yellow fever, namely vector control and vaccination.<sup>7</sup> The yellow fever vaccine 17D, derived from the Asibi parent strain, is a live attenuated virus grown in chick embryos. It was developed in the 1930s by Max Theiler, a South African born physician.<sup>8,9</sup> Widespread use of this vaccine has led to control of yellow fever in many endemic areas. A single dose induces long-lasting immunity, and the Advisory Committee on Immunization Practices (ACIP) recommends vaccination of persons nine months and older, travelling to, or resident in, endemic regions. The residents of endemic countries should be revaccinated every 10 years to maintain immunity. It is estimated that 100 million doses of the yellow fever vaccine are manufactured annually by six WHO-approved institutes globally.

Currently, yellow fever vaccination is an entry requirement for travellers to 127 countries, and it is also offered during mass vaccination and catch-up campaigns for routine use as part of the extended programme for immunisation (EPI) for infants in endemic countries.

## Tolerability and safety of yellow fever vaccines

Studies have indicated that the yellow fever vaccine is usually well tolerated by adults, and serious adverse events are rarely reported.<sup>9</sup> Early trials demonstrated that mild reactions occur five to eight days after vaccination in 10- 15% of vaccinees, with more severe reactions in only one to two per cent of cases.<sup>10</sup> Reactions vary from mild, comprising localised pain and erythema at the injection site, to headache, nausea, vomiting and diarrhoea. Systemic reactions are reported as

occurring in fewer than 0.2% of cases, although they may be more common than thought.<sup>11</sup>

Adverse events following immunisation (AEFI) are defined as signs or symptoms that follow the administration of a vaccine, and that are believed to be caused by the vaccine.<sup>12</sup> All AEFI are monitored by a passive surveillance system known as the Vaccine Adverse Event Reporting System, operated by CDC and the US Food and Drug Administration (FDA).<sup>13</sup> AEFI, following yellow fever vaccination, are typically mild and nonspecific.<sup>14</sup>

Interestingly, studies have suggested that there is a higher incidence of local inflammatory events in female vaccine recipients, than in males.<sup>14</sup> However, the gender effect was not found in relation to the yellow fever vaccine booster response.<sup>15</sup>

### Viscerotropic and neurotropic disease

Recent reports have indicated that the yellow fever vaccine can cause disease that resembles wild-type yellow fever virus infection, described as viscerotropic disease (YEL-AVD) and neurotropic disease (YEL-AND).<sup>16</sup> These complications occur in approximately 2.5 per one million vaccine doses, and may be as high as one in 40 000 doses in elderly (> 60 years old) vaccine recipients. Fatal adverse events appear to be associated with individual host factors controlling susceptibility, as well as with viral factors.<sup>16</sup> Host factors such as age (> 60 years), thymus disease (thymoma and thymectomy) and male gender, may be potential risk factors for the development of severe adverse events.<sup>9,17</sup> In general, the risk of YEL-AVD increases three- to fourfold in immunocompromised patients.<sup>18</sup>

#### *Yellow fever neurotropic disease*

In 1951 and 1952, the occurrence of post-vaccinal encephalitis in 15 infants from the UK, the USA, and France, formed the basis for the recommendation that excluded the use of 17D vaccine in infants under the age of six months.<sup>19</sup>

YEL-AND typically occurs in first-time vaccines, approximately two to 30 days post vaccination, and carries a case fatality rate of below five per cent. Between 1990-2004, 11 cases of YEL-AND were identified among US citizens. Four of these cases had post-vaccinal encephalitis, four had Guillain-Barré syndrome (GBS), and the remaining three had acute demyelinating syndrome. Most of these cases were benign and self-limiting.<sup>11</sup>

#### *Yellow fever viscerotropic disease*

YEL-AVD is a severe, acute illness with an incubation period of two to five days.<sup>15</sup> It is characterised by hepatitis, multi-organ failure, and high mortality, mimicking wild-type yellow fever in most respects, with viral antigen present in many tissues.<sup>14</sup> In endemic countries, the presence of the vaccine virus has to be confirmed by viral isolation, in order to distinguish it from wild-type virus.

Between 1996- 2001, nine cases of YEL-AVD were reported; four in the USA, four in Brazil, and one in Australia, eight of which were fatal. This passive surveillance may have underestimated the true number of cases due to underreporting.<sup>6</sup> Post-vaccination surveillance has subsequently been intensified in the USA and Brazil, as a result of the reported deaths. By May 2009, a further 51 cases had been identified since 2001.

Simultaneous administration of other vaccines and immunoglobulin might affect the rate of vaccine complications and response. It has been suggested that pre-travel immunoglobulin (given as prophylaxis for hepatitis A), co-administered with yellow fever vaccine, may previously have reduced vaccine-associated viscerotropic disease.<sup>20</sup> Also, when yellow fever vaccine was combined with typhoid fever vaccine, the subjects showed higher antibody titres to yellow fever than with yellow fever vaccine alone.<sup>18</sup>

As with wild-type yellow fever infection, the treatment of YEL-AVD is mainly supportive. According to the 2003 Surviving Sepsis Campaign management committee guidelines, the use of stress dose steroids (SDS) for the treatment of septic shock improves outcome.<sup>21</sup> Therefore, YEL-AVD is managed as septic shock by administering “intravenous hydrocortisone 200-300 mg/day, for seven days, in three or four divided doses, or by continuous infusion”. Hydrocortisone is preferred to dexamethasone. Oral fludrocortisone, 50 µg four times daily, may be utilised as an alternative to hydrocortisone.

### Precautions and contraindications

Because of the risks of adverse events, the yellow fever vaccine should not be administered to persons with severe chronic illness or immunodeficiency, those on immunosuppressive therapy, or who are pregnant. Persons with an egg allergy should also not be immunised as the vaccine is manufactured in chick embryos, and recipients may be at risk of severe hypersensitivity reactions.<sup>8,20</sup>

Infants and children are at the greatest risk of death following vaccination.<sup>22</sup> The yellow fever vaccine is not advised for use in infants below the age of nine months, except in active epidemics, where it has been used in infants who are as young as four months old.<sup>23</sup>

Five main considerations in determining the suitability of a patient for the yellow fever vaccination have been identified:<sup>9</sup>

- *Age:* In general, the yellow fever vaccine is contraindicated in infants below six months of age, and should be used with caution in infants between the ages of six and eight months. The yellow vaccine is considered safe for use in infants older than nine months. Persons above the age of 60 may be at a higher risk of side-effects following vaccination.<sup>17,22,24,25</sup>
- *Thymectomy and thymus disease:* Thymectomy and thymus disease are a contraindication for vaccination, as they increase the risk of YEL-AVD.<sup>26</sup>

- **Pregnancy:** The yellow fever vaccine is contraindicated in pregnancy, as its safety has not been well established. Although there has been no evidence of transplacental passage of the yellow fever vaccine virus, neutralising antibodies were found to have crossed the placenta, and were also found in the colostrum.<sup>27</sup> Teratogenicity was not noted in cases of inadvertent first trimester exposure to the yellow fever vaccine. Evidence has suggested a link with early gestational losses and spontaneous abortion.<sup>28,29</sup> However, the yellow fever vaccine may be given during unavoidable travel, or during an epidemic.
- **Immunosuppressed individuals:** Individuals who are immunosuppressed due to diseases, such as leukaemia and malignancy, or drugs, such as corticosteroids, have an increased risk of adverse events, and should not be vaccinated.<sup>30,31</sup> Human immunodeficiency virus (HIV) infected people who do not have acquired immune deficiency syndrome (AIDS) or have a cluster of differentiation 4 (CD4) > 200 mm<sup>3</sup>, may be vaccinated, although the neutralising antibody response is muted.<sup>32</sup> When HIV-infected patients are vaccinated, caution should be taken when the yellow fever vaccine is co-administered with the antiretroviral drug, maraviroc, as it can increase the risk for YEL-AVD.<sup>33</sup>
- **Allergy:** The yellow fever vaccine is contraindicated in persons who are hypersensitive to eggs, as it is produced in embryonated chicken eggs.

## Conclusion

The yellow fever vaccine has largely been demonstrated to be safe and well tolerated. However, surveillance systems for monitoring yellow fever activity in Africa remain poor and neglected. The strengthening of public health systems, in order to mitigate and reduce the impact of yellow fever outbreaks, remains critical. Reporting systems for side-effects must be improved, particularly in developing countries, in order to clarify the real risks of adverse events. This may be addressed through the education of healthcare workers, particularly professionals, e.g. doctors and nurses.

## Conflict of interest

Neither the authors have declared any conflict of interest that may arise from being named as an author of the manuscript.

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