

# Guideline: Preparing HIV-infected children and adolescents for travel

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## Summary

### **When to start talking about travel medicine?**

- Approach the general travel safety points in routine consultation
- Ask patients to come for review at least 6 weeks before they travel

### **What to cover:**

- Give general travel advice on avoiding road traffic accident, drowning incidents and on water and food hygiene
- Give prophylaxis for traveller's diarrhoea
- Explain ABCD of malaria prevention
- Recommend malaria personal protection measures
- Prescribe malaria prophylaxis
- Discuss the need for travel vaccines and refer to a travel service for vaccination by a travel medicine practitioner

## Introduction to the guideline

These guidelines do not replace a pre-travel consultation with a professional trained in travel medicine. They do cover the basics, and the additional considerations required for a HIV-infected traveller.

- The following website provides regularly updated country specific guidance for professionals: [www.nathnac.org](http://www.nathnac.org)
- Telephone advice can be gained from the National Travel Health Network and Centre (NaTHNaC) telephone advice line (0845 602 6712)

## General travel health and safety advice for travel

*The following advice for HIV-infected children and families planning to travel should be given in clinic:*

- Seek early expert advice when planning travel – at least 6 weeks before.
- If a child was recently started on antiretroviral therapy (ART) or their ART has changed, make sure it is tolerated prior to travel.
- Be up to date with routine UK vaccinations including catch up vaccinations – see CHIVA guidelines ([www.chiva.org/guidelines/iimmunisation](http://www.chiva.org/guidelines/iimmunisation)).

- Travel insurance is essential and is it essential to declare HIV. If any condition is not declared the insurer can refuse to cover for accidents as well as unrelated medical problems. Some insurance policies will not cover people living with HIV. Advice on travel and list of companies offering travel insurance for people with HIV can be obtained via the Terrence Higgins Trust ([www.tht.org.uk/myhiv/Your-rights/Travel](http://www.tht.org.uk/myhiv/Your-rights/Travel)). A company called 'It's So Easy Travel Insurance' ([www.hivtravelinsurance.com](http://www.hivtravelinsurance.com)) specialises in HIV travel insurance.
- Pack ART and any other medications in multiple bags, as if luggage is lost these medicines may not be available at destination
- As with any essential medication carry the prescription and a letter from the prescriber in case of border control.
- HIV positive visitors are still denied entry to some parts of the world, and restrictions vary depending on whether travel is short or long stay. View regulations by country at the global database on HIV specific travel ([www.hivtravel.org](http://www.hivtravel.org)).
- The Fit for Travel website provides generic travel health information for patients to access themselves: <http://www.fitfortravel.nhs.uk>

*Once the trip is planned, advise on following:*

- Road traffic accidents are the leading cause of death for all travellers, use car seats and seat belts for children as you would in the UK, be vigilant of vehicles whilst walking near the roadside.
- Drowning is the second leading cause of death in paediatric travellers. Children must be supervised when swimming in pools and must not dive until depth is established.
- Waterborne infections can result from swallowing water during swimming and water sports, although mainly through contaminated food and food hygiene. Avoid swallowing pool water and do not swim in water that may be contaminated with human or animal waste.
- Strict hand hygiene– wash with soap and water or alcohol based gel sanitizers if soap and water are unavailable. Drink boiled or bottled water where possible; avoid ice cubes and ice-lollies. Do not brush teeth using tap water. Treating water with chlorine can be as effective as boiling for preventing infections with most pathogens. Chlorine treatment should only be used when boiling is not possible, as it may not prevent cryptosporidium infection.
- Ensure food is clean and well cooked. Foods and beverages that are usually safe include steaming hot foods and drinks, fruits that are peeled by the traveller, unopened bottled beverages. Avoid buffets, raw fish and shellfish, raw fruits or vegetables that might have been washed in tap water. There is no evidence that following these rules reduces the risk of traveller's diarrhoea (TD), and prophylaxis and treatment of TD is described later.
- Discuss safe sex as appropriate. There is a high risk of first, and multiple, sexual partners in YP whilst travelling.

## Traveller's diarrhoea: prevention and treatment

Traveller's Diarrhoea (TD) affects up to 30% of patients travelling in high-risk areas, where hygiene standards are poor. When the traveller has an immunodeficiency resulting in increased risk of TD, a short course of *standby treatment* is warranted.

In addition *TD prophylaxis* is offered to selected travellers who are at risk of TD because of their medication or pre-existing morbidity. This includes those who require stable absorption of medications, and HIV positive children on ART may fit this category.

For standby treatment or prophylaxis the antibiotic choice should cover *E. Coli/ ETEC/ Salmonella/ Shigella* and *Campylobacter* species. Co-trimoxazole can reduce TD risk and it is preferred prophylactic antibiotic by HIV specialists. Co-trimoxazole was showed to be effective in preventing bacterial infections despite widespread resistance (1). Some Travel medicine experts prefer azithromycin prophylaxis which is given daily for TD prevention. TD is an **unlicenced** but commonly utilized indication for azithromycin prophylaxis. Drug interactions with antiretrovirals should be checked, see [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org).

### *For patients taking standby treatment or prophylaxis:*

- Advise to seek medical care in the event of bloody or mucus containing stools, severe abdominal pain, or diarrhoea with fever.
- Advise also about the need for oral rehydration solutions.
- Warn those travelling to risk areas (Asia/ Africa) regarding the fluctuating diarrhoea and constipation picture of typhoid fever.

## Malaria prevention

Malaria is caused by *Plasmodium* parasites and is transmitted by many species of *Anopheles* mosquitoes, which bite between dusk and dawn. Five *Plasmodium* species infect humans. The table below shows the prevalent species on each continent.

Plasmodium Species	Main Continent(s)	Dormant stage and possibility of relapse
<i>P. falciparum</i>	Africa / Pacific	No
<i>P. knowlesi</i>	Malaysia and SE Asia	No
<i>P. ovale</i>	West Africa, Western Pacific	Does occur
<i>P. vivax</i>	Asia, Far East, North Africa, Central and South America, Pacific	Does occur

<i>P. malariae</i>	Africa	No
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*Plasmodium vivax* is the most common malaria parasite overall and it causes much long-term morbidity in Southeast Asia due to its ability to remain dormant in the liver and recrudescence.

*P. falciparum* and *P. knowlesi* can lead to fatal infection due to their rapid cycles of multiplication in non-immune individuals. *P. falciparum* causes the most morbidity and mortality worldwide.

Travellers can be at risk of malaria infection in Africa, Asia, the Americas and the Pacific region. The National Travel Health Network and center (NaTHNac) has country specific guidelines ([www.nathnac.org](http://www.nathnac.org)). Risk varies significantly within countries and a risk assessment can be sought from a travel medicine professional at a Hospital for Tropical Diseases.

People who formerly lived in malaria endemic countries may believe that they are immune, and therefore, do not need to take malaria preventative measures. They remain at high risk of infection as they are likely have lost any protective immunity within 6-12 months after leaving endemic regions, yet are least likely to use prevention methods. The risk of severe malaria must be stressed to these families.

### *Malaria in HIV positive children*

Requirements for malaria prevention are the same for patients living with and without HIV. However studies show that HIV positive individuals are more likely to suffer severe malaria and that the risk of clinical malaria increases with decreasing CD4 count in adults. This may not be the case for malaria immune individuals where HIV is fully suppressed on ART, but a small study of HIV positive African adults still reported higher parasitaemia and more severe malaria despite ART(2). In view of these findings prevention of malaria might be regarded as even more vital in HIV positive travellers.

In terms of advising parents and young people about malaria you should explain the four principles – the **ABCD** – of malaria protection, whereby travellers should:

1. Be **Aware** of the risk, the incubation period (malaria may present as fever 7 days or more after entering endemic areas), the possibility of delayed onset (up to 12 months), and the main symptoms. In children symptoms of malaria are non-specific including fever, cough, coryzal symptoms and vomiting/diarrhoea.
2. Avoid being **Bitten** by mosquitoes, especially between dusk and dawn. This means using personal protection such as wearing protective clothing or repellents from dusk till dawn, and sleeping under treated bed nets.
3. Take **Chemoprophylaxis** as prescribed.
4. Seek **Diagnosis** and treatment if a fever develops 1 week or more after entering a malaria risk area and up to 12 months after departure, explaining to the healthcare professional that they have been at risk of malaria.

To avoid being bitten, you need to advise patients entering malaria endemic areas to use *personal protection* as well as *chemoprophylaxis*.

## Personal protection

- Mosquito repellents
- Protective clothing
- Bed nets

### Mosquito repellents

A repellent containing 30-35% DEET reduces the risk of many vector borne diseases, including malaria. This is safe from 2 months of age (children under 2 months should be fully covered with cot nets or in a screened room after dusk instead). DEET spray or lotion should be reapplied to exposed skin every 6 hours, more frequently if they have been swimming or are sweaty. In younger children take care not to put on the hands, which they may put into their mouths or eyes.

Other repellents such as PMD (P-METHANE 3,8- DIOL) are also licensed in children over 3 years.

### Protective clothing

Children should wear long clothes to cover wrists and ankles, which are favoured biting sites, from dusk until dawn, and if this is not possible they should retire to a screened room at dusk. Permethrin treated clothing is safe for children.

### Bed nets and cot covers

Bed nets reduce malaria risk by approximately 50% (3). They should be well maintained without holes and tucked into the mattress. Insecticide treated nets are preferable and they need to be retreated every 6 months. Carrycot and pram net covers should be utilised for infants.

## Chemoprophylaxis

Consideration must be given to possible drug-drug interactions in patients receiving chemoprophylaxis with antiretroviral medicines and/or other prophylactic medicines used in HIV-infection. There are 3 main options available for malaria prophylaxis:

- Malarone
- Mefloquine
- Doxycycline

Other options (such as chloroquine and fansidar) may be prescribed by travel medicine specialists, for specific itineraries.

The Advisory Committee on Malaria Prevention (ACMP 2015) recommend to discuss options for chemoprophylaxis with the traveller's own HIV physician who should make the decision on choice of agent so as to reduce risk of toxicity and interactions which may affect HIV resistance.

### Important interactions between antimalarials and ART

For full details on drug-drug interactions, refer to the University of Liverpool HIV drug Interactions site ([www.hiv-druginteractions.org](http://www.hiv-druginteractions.org))

Protease Inhibitors (PIs) as well as non-nucleoside reverse transcriptase inhibitors (NNRTIs) induce liver enzymes that may be involved with elimination of malaria prophylaxis drugs. Potentially this could impact on metabolism of the antimalarial or the ART, though the extent and the clinical significance is often unclear.

- Mefloquine plasma concentrations are affected by inducers or inhibitors of the isoenzymes CYP3A4 and CP450, such as rifampicin and efavirenz, which may lead to altered mefloquine levels.
- Malarone®: atovaquone and proguanil plasma concentrations may be reduced (38-75%) when given with NNRTI's or PI's, the significance of this is uncertain. Taking the tablet with a fatty meal may increase bioavailability. Some travel experts may recommend to increase the dose of malarone in children over 5 kg. This is off license and should be discussed with an expert in Travel medicine-
- Doxycycline is the simplest agent for older children on ART as it has no known interaction with ARVs. It is not recommended for this indication in children under 12 years, however if other antimalarial prophylaxis cannot be used, doxycycline can be considered in younger children with specialist advice.

**Table 1 Prescribing considerations for malaria chemoprophylaxis in children taking ART (4, 5)**

Drug	Reasons you might consider using this drug	Reasons you may avoid using this drug	Additional considerations for use in children with HIV infection
Atovaquone/ Proguanil (Malarone®) paediatric formulation	<ul style="list-style-type: none"> <li>▪ Good for last-minute travellers because the drug is started 2 days before traveling to a malarious area</li> <li>▪ Some people prefer a daily medicine</li> <li>▪ Good choice for shorter trips because you only have to take the medicine for 7 days upon return</li> <li>▪ Paediatric tablets are</li> </ul>	<ul style="list-style-type: none"> <li>▪ Not licenced for children under 5kg bodyweight.</li> <li>▪ Cannot be taken in severe renal impairment</li> <li>▪ More expensive than the other options (especially problematic for trips of long duration)</li> <li>▪ Some children would rather not take a medicine every day</li> <li>▪ Causes GI side effects</li> </ul>	<ul style="list-style-type: none"> <li>▪ Malarone® increased Zidovudine AUC by ~35% but had no effect on Malarone® exposure</li> <li>▪ Coadministration can increase risk of haematotoxicity so use with caution and monitor full blood count</li> <li>▪ The AUC of atovaquone and proguanil were significantly lower in patients on atazanavir, ritonavir, lopinavir, or efavirenz</li> </ul>

Drug	Reasons you might consider using this drug	Reasons you may avoid using this drug	Additional considerations for use in children with HIV infection
	available	<p>particularly nausea and diarrhoea.</p> <ul style="list-style-type: none"> <li>Relatively expensive (~£2 per tablet)</li> </ul>	<ul style="list-style-type: none"> <li>The decrease in proguanil exposure has been attributed to possible induction of CYP2C19 and other boosted PIs could reduce malarone exposure via the same mechanism</li> <li>Counsel to take malarone with high-fat meals to increase its bioavailability, consider increased dose with specialist</li> </ul>
Doxycycline	<ul style="list-style-type: none"> <li>Some people prefer a daily medicine</li> <li>Good for last-minute travellers because the drug is started 2 days before traveling to an area where malaria transmission occurs</li> <li>One of the least expensive antimalarials (~ £1.30 per tablet)</li> <li>Some teenagers are already taking doxycycline chronically for prevention of acne; they do not have to take an additional medicine</li> <li>Doxycycline also can prevent some additional infections (e.g., Rickettsiae and leptospirosis) and so it may be preferred by people planning to do hiking, camping, wading or swimming in fresh water</li> </ul>	<ul style="list-style-type: none"> <li>Some people would rather not take a medicine every day</li> <li>Not licenced for <u>children &lt;12 years old</u> for prophylaxis</li> <li>Cannot be used in children with porphyria</li> <li>For trips of short duration, some people would rather not take medication for 4 weeks after travel</li> <li>Girls prone to vaginal yeast infections when taking antibiotics may prefer taking a different medicine</li> <li>Persons planning on considerable sun exposure may want to avoid the increased risk of sun sensitivity</li> <li>Causes gastrointestinal side effects particularly oesophagitis and gastritis when not taken with food</li> <li>Oral vaccinations of live bacteria may be attenuated and should therefore be completed at least 3 days before the first dose of doxycycline</li> </ul>	<ul style="list-style-type: none"> <li>Antacids may impair doxycycline absorption thus buffered tablet formulations of didanosine, which contain antacids and should be spaced from doxycycline</li> </ul>
Mefloquine (Lariam®)	<ul style="list-style-type: none"> <li>Some people would rather take a weekly medicine</li> <li>Good choice for long trips because it is taken only weekly</li> <li>One of the cheapest antimalarials (~ £1.30 per</li> </ul>	<ul style="list-style-type: none"> <li>Cannot be used in patients with psychiatric conditions</li> <li>Cannot be used in patients with seizure disorders</li> <li>Cannot be used in cardiac</li> </ul>	<ul style="list-style-type: none"> <li>Rilpivarinine affects the QT interval and cannot be used with mefloquine</li> <li>Darunavir and ritonavir potentially increase mefloquine exposure</li> <li>Mefloquine may reduce the</li> </ul>



Drug	Reasons you might consider using this drug	Reasons you may avoid using this drug	Additional considerations for use in children with HIV infection
	<ul style="list-style-type: none"> <li>week)</li> <li>▪ Can be used during pregnancy</li> <li>▪ More experience of use in babies than other antimalarials</li> </ul>	<ul style="list-style-type: none"> <li>conduction abnormalities- mefloquine is felt to be safe in Congenital Heart Disease as long as the child has never had arrhythmias</li> <li>▪ Cannot be used in areas with mefloquine resistance</li> <li>▪ Not a good choice for last-minute travellers because drug needs to be started at least 2 weeks prior to travel</li> <li>▪ For trips of short duration, some people would rather not take medication for 4 weeks after travel</li> </ul>	<ul style="list-style-type: none"> <li>ritonavir AUC by 31% so should be used cautiously with ritonavir</li> <li>▪ Mefloquine does not inhibit or induce cytochrome P450 itself but CP450 inducers such as efavirenz, may alter mefloquine plasma concentration. The clinical consequences of these effects are unknown</li> </ul>
Primaquine	<ul style="list-style-type: none"> <li>▪ Is the most effective medicine for preventing <i>P. vivax</i> and is used for travel to places with &gt; 90% <i>P. vivax</i></li> <li>▪ May be used alongside falciparum prophylaxis, where falciparum prophylaxis is also required</li> <li>▪ Good for last-minute travellers to these areas because the drug is started 1-2 days before travel (continued for 7 days upon return)</li> <li>▪ Very expensive (£2-3 per day)</li> </ul>	<ul style="list-style-type: none"> <li>▪ Unlicensed in children</li> <li>▪ Can cause fatal haemolysis in G6PD deficiency. Cannot be used in patients with glucose-6-phosphatase dehydrogenase (G6PD) deficiency or patients who have not been tested for G6PD deficiency</li> <li>▪ There are costs and delays associated with getting a G6PD test done; however, it only has to be done once. Document G6PD status before prescribing</li> <li>▪ Cannot be used in pregnancy</li> <li>▪ Cannot be used during breastfeeding unless the infant is also negative for G6PD deficiency</li> <li>▪ Can cause GO side effects especially when not taken with food</li> </ul>	<ul style="list-style-type: none"> <li>▪ The metabolism of primaquine produces oxidative metabolites, which are primarily responsible for the haemolytic effect of primaquine.</li> <li>▪ Nevirapine, zidovudine and efavirenz could potentially increase the amount of haemotoxic metabolites. Caution should be used when combining these drugs and full blood count should be monitored</li> </ul>

- Use this table for prescribing guidance; always check drug interactions before prescribing, as more up to date information may be available: [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)
- Always check the length of prophylaxis required before and after the trip and the weight based doses in the BNFC: [www.bnf.org](http://www.bnf.org)
- Always check how best to take the medicines in the BNFC

## Vaccines for travel

For up to date guidance on vaccination please refer to the current version of the Immunisation against infectious disease: the Green Book ([www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book](http://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book))

### *Background*

Vaccine immunogenicity can be reduced in HIV-infected individuals and may wane more rapidly, heightening the need for revaccination. Inactivated vaccines can be used just as they would be used for HIV–uninfected individuals anticipating travel. However, they may be less effective, especially at lower CD4 counts, and the duration of immunity may be reduced.

Care needs to be taken with live vaccines, especially in children with CD4 of <15%.

**Oral typhoid and oral polio vaccine are absolutely contraindicated for all travellers with HIV.**

### *Routine UK vaccinations*

Children and young people should be up to date with the UK schedule of vaccination – see CHIVA guidance for routine vaccinations ([www.chiva.org/guidelines/iimmunisation](http://www.chiva.org/guidelines/iimmunisation)).

### **Influenza**

Influenza viruses are the commonest travel related vaccine preventable diseases. Seasonal Influenza is spread via droplets during close crowding in buses, trains airports and other travel situations. People living with HIV have increased rates of complications from influenza. The inactivated parenteral vaccine is safe for HIV positive children and annual vaccination is recommended for those over 6 months. The live intranasal influenza vaccine may be used alternatively in children aged >2years.

### **Hepatitis A**

Hepatitis A virus is transmitted by ingestion of faecally contaminated food and water, and occasionally by close contact between children. The distribution of hepatitis A is closely mapped to poor sanitary conditions, with the highest incidence in the Indian subcontinent.

Hepatitis A vaccine is an inactivated vaccine and is safe in HIV-infected children. The vaccine is recommended for children over 5 who have spent their infancy in non-endemic areas and are travelling where hepatitis A is prevalent. Vaccination should ideally be 14 days prior to travel.

Immunological response to hepatitis A vaccine correlates with CD4 T-cell counts at immunisation. A lower CD4 cell count and a higher HIV viral load are associated with a lack of response to vaccine, with less than half of HIV-infected adults responding to a single dose (6).

To achieve maximum benefit from hepatitis A vaccination, children should be vaccinated when they have achieved optimum immune reconstitution on ARVs.

One dose provides protection for a year and a second dose at 6 months provides protection for at least 20 years in HIV negative individuals. The efficacy in HIV-infected children is lower (7), especially with lower CD4 counts, as it is in adults (8). Children with low CD4 counts may benefit from further doses, this is best assessed with serology. The duration of protection in HIV positive children is known to wane between two and five years (9) with some recommending boosters dependent on serology and some recommending booster doses every 5-10 years. There is no evidence to choose one strategy over the other.

## Hepatitis B

The World Health Organization (WHO) maps the prevalence of hepatitis B to be highest in Asia and Africa. HIV-infected people are more likely to develop HBV viraemia when infected and have a 3- to 6-fold higher risk of becoming chronic carriers of hepatitis B.

As an inactivated vaccine, hepatitis B vaccine is safe and recommended for all HIV-infected patients routinely, and especially prior to travel to a high-risk area if it has not already been given.

Both hepatitis A and B vaccines are part of routine vaccination for HIV positive children. If both are needed then a combined vaccine (eg. Twinrix) should be used). There is also no harm of giving combined vaccine to a child who has immunity against HAV due to past infection or HAV vaccination, as there is some evidence that HAV/HBV combined vaccine provides enhanced HBV immunogenicity. See CHIVA guidance for routine vaccinations ([www.chiva.org/guidelines/iimmunisation](http://www.chiva.org/guidelines/iimmunisation))

Vaccines for overseas travel

Travel vaccines should be given on the advice of a travel medicine service. The prescription of travel vaccines depends on a thorough risk assessment, which includes the country visited, the season, length of stay, traveller activities, risk perception and preference. The following vaccines may be indicated.

## Typhoid

*Salmonella typhi* and *paratyphi* A/B/C are serotypes of *Salmonella enterica*.

Infection occurs by ingestion of contaminated food and water, or by direct faeco-oral transmission in areas of poor sanitation. The disease is endemic throughout Africa and South America but most cases occur from Travel to Asia, with India, Bangladesh and Pakistan accounting for 95% of infections imported to the United Kingdom. Children visiting friends and relatives suffer a high proportion of cases and should be targeted for vaccination.

HIV positive patients are at particularly high risk of all salmonella infections and may have severe disease with bacteraemia, and relapsing infections. For children living with HIV,

vaccination should be considered for all risk areas including Asia, Sub-Saharan Africa and South America.

### **Choice of vaccine and schedule**

The oral typhoid vaccine is contraindicated in HIV. Immunization should be with intramuscular inactivated Vi polysaccharide vaccine. There are two licensed vaccines (Typhim Vi and Typherix), which are safe, and if CD4<sup>+</sup> T-cell counts are above 200 cells/mm<sup>3</sup>, the immunogenicity is adequate, with a booster recommended every 3 years(10). Neither of the licensed vaccines is suitable for children under 2 years of age as neither elicits protective responses, as expected for a polysaccharide vaccine in this age group. In older children this vaccine still provides only moderate protection of approximately 60% (11) and does not protect against *S. paratyphi*. All travellers should therefore be advised on personal and food hygiene.

### **Rabies**

Rabies is caused by a Lyssavirus, transmitted by the bite, scratch or secretions of a rabid animal, nearly always a dog. Rabies is present across Africa, Asia, America and Europe, with the highest prevalence in countries with feral dogs and no rabies control measures in place.

Only an estimated 0.4% of travellers experience a bite per months stay in an endemic country and the disease is rare in travellers, however, children may put themselves at risk when handling animals and children hold the highest bite burden, with 40% of rabies post exposure prophylaxis (PEP) being accessed for child travellers (12). And rabies is invariably fatal once symptoms develop. Children who make a long visit or multiple visits to countries with endemic rabies should be offered pre exposure rabies vaccine (13).

### **Helping parents decide about pre-exposure rabies vaccine**

The primary course of rabies vaccine is costly; it consists of 3 doses of vaccine at day 0, 7 and 28. The third dose can be given early at day 21 if there is insufficient time before travel. The pre exposure vaccine is often described as 'insurance' because having the pre-exposure vaccine course eliminates the need for post-exposure rabies immunoglobulin (RIG), which is in short global supply and often necessitates repatriation to the nearest developed country, which is expensive and disrupts the holiday. Children who have had the pre exposure vaccine course prior to travel will still require further booster doses of rabies vaccine when a significant bite/scratch occurs, but will not require RIG.

### **Choice of vaccine and schedule**

Approximately 95% of HIV negative adults will respond to a full course of rabies pre exposure vaccine, and the antibodies are long lived. In HIV positive adults a reduced response to vaccination occurs, particularly in those with lower CD4 counts, and there is no data for HIV positive children. If HIV positive children receive this vaccine as pre-exposure prophylaxis antibody titres could be checked 2 weeks after the last vaccine dose and those with titres <0.5 IU/ml offered a booster followed by repeat serology testing (14). Rabies serology is available at

a select few UK laboratories and advice is sought via the PHE Rabies clerk (on +44 (0)208 3276204).

## Yellow fever (YF)

Yellow fever (YF) virus is a flavivirus, transmitted by day-biting *Aedes* mosquitoes, in tropical and sub-tropical regions of Africa and South America. There is no YF in Asia.

### Yellow fever vaccination requires specific consideration because:

1. YF is a severe disease with a high morbidity and mortality
2. YF is subject to international Health Regulations, with a formal requirement for certificate for entry into certain countries (in such situations, it must be administered more than 10 days prior to entry to comply with International Health Regulations (IHR's))
3. YF is a live vaccine and has been associated with serious adverse events particularly in individuals who are immunocompromised.

The list of countries requiring YF vaccination certificate (or exemption certificate) for entry can be found on the WHO website (<http://www.who.int/ith/yellow-fever-risk-mapping/en/>). The designation of a country to require certification for YF vaccination may not reflect the risk in the country however. It may actually reflect the absence of the disease in that country and attempts to mitigate spread. This is important to consider where contraindications to vaccination apply.

### Choice of vaccine and schedule

The only licensed YF vaccine is a live attenuated 17D strain of yellow fever virus grown in chick embryos. Even for HIV-uninfected individuals this vaccine YF is considered to be the most dangerous vaccine in current use because it is associated with severe adverse events: Yellow Fever Associated Viscerotropic disease (YEL-AVD) and Yellow Fever Associated Neurologic Disease (YEL-AND).

Infants aged <6-9 months must not be given yellow fever vaccine because of the risk of YEL-AND encephalitis. There is a theoretical increased risk of both these adverse events in HIV-infected children.

### Contraindications

Travellers with asymptomatic HIV infection and adequate CD4 counts pose a relative contraindication and those who cannot avoid potential exposure to yellow fever, for example when travelling into an epidemic, should be offered vaccination. They should ideally have a high CD4 count, a low VL and be on ART. The need to vaccinate in this group must be made using a careful risk assessment including seasonality, transmission intensity, and length of stay. The risk is of catching YF is significantly higher in Africa than South America (15) and during epidemics. The decision must be made with the carers' full comprehension of the adverse event profile, and with full, informed parental consent. Personal protective measures must still be used.

No large prospective, randomized trials have been performed to address the safety, or efficacy of YF vaccine adequately amongst HIV-infected children. In terms of vaccine efficacy, retrospective data provide cautious support for the safety and moderate efficacy of YFV vaccination in HIV-infected adults with CD4 counts over 15% (16, 17), but symptomatic HIV infection or CD4 <15% (or <200) is currently an absolute contraindication for vaccine administration.

In HIV-infected infants the efficacy appears low with less than a quarter responding to the vaccine (18). If travel to a yellow fever zone is absolutely necessary and vaccination is not administered, then patients should be advised of the risk level, instructed in methods for avoiding bites, and provided with an exemption certificate.

In HIV negative persons a single dose of vaccine is legally valid for life but the duration of protection is unknown. All children vaccinated or not, must take bite precautions in the daytime to avoid YF in endemic regions.

YF vaccination and YF exemption certificates can only be provided by registered YF vaccination centers in the UK. The vaccine is administered as a deep subcutaneous injection. YF vaccine and MMR should be separated by 30 days as co-administration affects immunogenicity. See recommendations for administration of more than one live vaccines:

[https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/422798/PHE\\_recommendations\\_for\\_administering\\_more\\_than\\_one\\_live\\_vaccine\\_April\\_2015FINAL\\_.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/422798/PHE_recommendations_for_administering_more_than_one_live_vaccine_April_2015FINAL_.pdf)

### **Japanese encephalitis (JE)**

Japanese encephalitis (JE) is caused by the eponymous Flavivirus, which can cause severe viral encephalitis in children. JE is transmitted from pigs and birds by *Culex* mosquitoes, which are evening and night-time biting mosquitoes. The disease is present in Asia and the Pacific with most transmission in agricultural areas of Asia where there are flooded rice paddy fields, and pig farms. There is a small amount of urban transmission.

The risk to most travellers is very low with estimated incidence of less than one case per million travellers (19) and the mainstay of JE prevention is bite avoidance after dusk; using personal protective measures such as mosquito repellent, long-clothes, and sleeping under an insecticide treated mosquito net. These precautions should be used instead of the vaccine in many cases. An inactivated vaccine may sometimes be recommended for children over 2 months of age, travelling to high-risk rural areas during transmission season. Expert risk assessment is advised.

### **Choice of vaccine and schedule**

IXIARO® vaccine contains an inactivated virus strain and it is the only licensed vaccine in the UK. The IXIARO® primary course consists of 2 doses given one month apart. This primary course should be completed at least one week prior to exposure. The majority of HIV-infected children with immune recovery on ART develop protective antibody after JE revaccination and no amendments are made to the schedule for HIV-infected children at present. No long-term

paediatric data has been generated but adults demonstrate continued protection for up to 3 years. As such, a booster dose is recommended for all age groups within the second year if continued protection is going to be required.

Live attenuated JE vaccines, available in other countries are contraindicated in HIV.

## Cholera

Cholera is a bacterial diarrhoeal illness caused by consuming water or food (often shellfish) contaminated with toxigenic *Vibrio cholerae*. Person-to-person spread may occur through the faeco–oral route and so preschool children in are particularly affected during outbreaks. Cholera is present in countries with poor sanitation and food hygiene, worldwide. British travellers rarely acquire cholera but most imported cases are from the Indian subcontinent (20).

The cholera vaccine confers protection against *Vibrio cholerae* serogroup 01 only. It does not protect against serogroup 0139 or other vibrio species. The reported protective efficacy against serogroup 01 cholera is only around 68% and this begins to wane around 6 months post-vaccination (21), and as such the mainstay of prevention is food and water and hand hygiene. For most travellers cholera vaccination is not recommended. Vaccination is occasionally considered, if a child is going to live in unsanitary conditions, where they will be drinking untreated water, or to areas with a recent outbreak.

### Choice of vaccine and schedule

The oral cholera vaccine is inactivated and is felt to be safe for HIV-infected people. An effectiveness study in a population with high HIV prevalence showed similar protection as in other populations (24), and an adult trial showed a positive relationship between CD4 count and vaccination response, those with normal CD4 levels having reasonable response.

The inactivated oral vaccine licensed in the UK is named Dukoral. The vaccine is supplied as granules, with a separate bicarbonate buffer suspension, which protects the vaccine from destruction by gastric acid. Food and drink should be avoided for one hour before and one hour after. The primary vaccination course consists of oral vaccination on day 0 and again 6 weeks later in children over 6 years. Children between 2-6 years receive a third dose between one and six weeks after the second dose. If more than 6 weeks lapse between doses, the primary course should be recommenced. For continued protection a single booster dose is recommended 2 years after completing the primary course for children over six years of age, and six months after completing the primary course for children aged two to six years.

HIV-infected children may be considered for cholera vaccination, seek specialist advice.

## Meningococcal ACWY vaccine

HIV-infected paediatric travellers who visit the meningitis belt of sub-Saharan Africa during the dry season (December–June) should be vaccinated with a quadrivalent conjugate meningococcal ACWY vaccine. The Government of the Kingdom of Saudi Arabia also requires

that all travellers (over 2 years) to Umrah or Hajj receive this vaccine and provide documentation of vaccination in the 3 years prior to travel.

### **Choice of vaccine and schedule**

This is an inactivated vaccine and is safe in HIV-infected children. It is recommended that ACWY conjugate vaccine (Menveo® and Nimenrix®) be used in HIV-infected children rather than ACWY polysaccharide vaccines in order to generate better immune responses. The immunogenicity and safety of meningococcal conjugate have been reported in a large study, which showed response rates from 55-86% across the different serogroups, with higher response rates in those with higher CD4 cell counts and lower viral load (22). Response rates increased with a second dose of vaccine and so 2 doses are advised.

HIV-infected children will have already received this vaccine within the routine schedule. If this vaccine has already been given then a second dose should be given (no less than 8 weeks after the first dose). If a child received 2 doses this should be boosted 3 years later (if the last dose was received before age 7), or, 5 years later (if the last dose was received at/after age 7) (23).

### **Tick-borne encephalitis (TBE)**

Tick borne encephalitis (TBE) is caused by a flavivirus, transmitted to humans by the bite of an infected tick or, less commonly, by ingestion of unpasteurized milk from infected animals such as goats. Infections occur in many parts of Europe, the former Soviet Union and Asia, corresponding to the distribution of the tick reservoir.

There are two seasonal peaks in central Europe, one in June/July and the second in September/ October.

It is not known whether the natural history of TBE is modified by HIV infection.

The TBE vaccine should be offered to HIV-infected persons in the same situations as HIV-uninfected persons. That is those who intend to walk or camp or live in heavily forested regions of affected countries during late spring or summer, when the ticks are most active.

### **Choice of vaccine and schedule**

TicoVac® is the only available vaccine for TBE. It is a whole virus inactivated vaccine, which is safe in HIV. Adult studies suggest the vaccine may be less immunogenic in HIV positive people (24). Decisions about boosting for repeat trips can be made using serology and the protective antibody response is considered to be >126 Vienna units per ml (VIEU/ml) (25).

The vaccine course consists of 3 doses, the first on day 0, the second 1-3 months after the first, and the third 5-12 months after the second. An accelerated course is possible. To achieve immunity before the beginning of the seasonal tick activity, which is in spring, the first and second dose should preferably be given in the winter months.



## Prevention of non-vaccine preventable diseases

Dengue, Zika and Chikungunya are viral illnesses spread by *Aedes* mosquitoes, which feed primarily in the daytime. Mosquito repellents are required both day and night in areas where these diseases occur.

### Dengue

Most cases are from Asia, the Americas and the Caribbean although the geographical distribution is spreading. Although there are licensed vaccines, none is available for travellers at present and the mainstay of prevention is awareness and bite avoidance, this means the use of repellents particularly in the daytime. A small case series of HIV positive adults with Dengue infection showed no increase in pathogenicity (26).

### Zika

Zika is a Dengue-like viral infection. Transmission is unstable and currently an epidemic is spreading throughout the Caribbean and South America. In addition to mosquito borne transmission, there is a low risk of sexual transmission and barrier methods should be advised for all travellers visiting endemic areas. Pregnant women should avoid non-essential travel due to the association between Zika viraemia and neonatal microcephaly. There is no licensed vaccine. Currently there is no evidence of more severe infections in HIV-infected individuals.

### Chikungunya

Chikungunya occurs in the Pacific, Caribbean, South America and Asia. There is no vaccine. There is no evidence that Chikungunya infection is more severe in HIV or worsens HIV viral load or CD4 count (27).

### Viral Haemorrhagic Fever (VHF)

Viral haemorrhagic fever (VHF) is a general term for a severe viral illness, associated with bleeding. The term is usually applied to disease caused by *Flaviviridae* (yellow fever, dengue, Omsk haemorrhagic fever, Kyasanur forest disease), *Arenaviridae* (Lassa fever, Junin and Machupo), *Bunyaviridae* (Crimean-Congo haemorrhagic fever, Rift Valley Fever, Hantaan haemorrhagic fevers) and *Filoviridae* (Ebola and Marburg). VHFs have a high case-fatality rate. The recently published Ebola virus vaccine (Live vaccine: rVSV-ZEBOV) trial demonstrated excellent Ebola protection but this vaccine is not currently available for tourists.

HIV-infected paediatric patients returning from countries endemic to VHFs should be encouraged to report signs of infection and these patients should be managed as per national guidelines.



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