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BRITISH HIV ASSOCIATION GUIDELINES

British HIV Association guidelines for immunization of HIV-infected adults 2008

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1.0 Introduction

These guidelines provide evidence-graded recommendations on the appropriate use of active and passive immunization in HIV-infected adults. There are several factors that make the formulation of HIV-specific immunization guidelines important at a time when highly active antiretroviral therapy (HAART) is modifying the natural history of HIV infection, vaccination practices are changing and new vaccines are becoming available in clinical care.

Compared with healthy individuals, HIV-infected adults may have an increased risk of infection or experience more severe disease following exposure to vaccine-preventable diseases. As a result, a lower threshold for recommending immunization may be indicated relative to the general population. Responses to vaccination are often sub-optimal in HIV-infected persons, who may benefit from higher or more frequent vaccine doses. Furthermore, reduced rates and durability of responses may require more frequent use of serological testing than is generally recommended, in order to determine antibody levels after vaccination and guide boosting requirements.

As a result of improved health and prognosis, HIV-infected persons are increasingly likely to engage in exposure-prone activities related to occupation or travel, and may require vaccines that are traditionally contra-indicated in immunocompromised persons but may be safe to use in HIV-infected persons with restored immunity. Safety of vaccination remains an important consideration. Inactivated vaccines can be used safely in HIV-infected persons if indicated (Table 1). In some cases, the increased risk of adverse reactions either contraindicates the use of certain vaccines or restricts them to HIV-infected persons

Table 1 Inactivated vaccines that may be used safely in all HIV-infected adults if indicated

Vaccine	Indication	Common use
Anthrax	RS	Occupational
Cholera (WC/rBS)	RS	Travel
Hepatitis A	RS	Risk groups
Hepatitis B	R	
Haemophilus influenzae	RS	Risk groups
Influenza-parenteral	R	Indications are strengthened in the presence of additional risk factors
Japanese encephalitis	RS	Travel
Meningococcus (MenC)	RS	Risk groups
Meningococcus (ACWY)	RS	Travel
Pneumococcus (PPV23)	R	Indications are strengthened in the presence of additional risk factors
Rabies	RS	Travel
Tetanus-diphtheria-parenteral poliomyelitis (Td/IPV)	RS	Uncertain vaccination status or travel
Tick-borne encephalitis	RS	Travel
Typhoid (ViCPS)	RS	Travel

R, recommended in all; RS, recommended in selected groups.

Table 2 Live vaccines that may be indicated in HIV-infected persons, but should not be used if the CD4 count is <200 cells/μL

Vaccine
Measles, mumps, rubella (MMR)
Varicella
Yellow fever

Table 3 Live vaccines contraindicated in all HIV-infected adults regardless of CD4 cell count

Vaccine	Comment
Cholera (CVD103-HgR)	
Influenza (intranasal)	Also contraindicated in close contacts
Oral poliomyelitis (OPV)	Also contraindicated in close contacts
Typhoid (Ty21a)	
Tuberculosis (BCG)	
Smallpox (Vaccinia)	Exceptions apply (see section 16.0)

with good immune function. Traditionally, live vaccines have been contraindicated in HIV infection. However, HAART-induced immunoreconstitution is either known or expected to reduce the risk of adverse events, in many cases shifting the risk–benefit ratio in favour of vaccination. Important examples of live vaccines that can be used cautiously in HIV-infected persons include those for measles, mumps and rubella (MMR), varicella and yellow fever (Table 2). Other live vaccines remain contraindicated, either because safer inactivated alternatives are available (e.g. typhoid) or because of a lack of safety data and uncertainty about vaccine efficacy [e.g. Bacille Calmette–Guerin (BCG)] (Table 3).

Table 4 Vaccines recommended for HIV-infected adults found to be susceptible upon serological screening

Vaccine	CD4 count (cells/μL)	Comment
Hepatitis B	Any	
Measles, mumps, rubella (MMR)	>200	All measles IgG seronegative persons; rubella IgG seronegative women of child-bearing age
Varicella	>400 Also consider if >200	All VZV IgG seronegative persons

Table 5 Vaccines recommended for HIV-infected adults who have missed routine childhood vaccinations or have uncertain vaccination history

Vaccine	Group	CD4 count (cells/μL)	Comments
Tetanus-diphtheria/ parenteral poliomyelitis (Td/IPV)	All	Any	Complete a five-dose course regardless of the interval since the last dose and the type of vaccine received previously
Meningococcus-MenC	Adults <25 years	Any	

Tables 4–6 summarize the recommendations for pre-exposure prophylaxis. Table 7 summarizes the recommendations for travel-related vaccination. Table 8 summarizes the recommendations for post-exposure prophylaxis. The reader should refer to the specific sections for further details.

Because there is a paucity of controlled studies to inform the formulation of HIV-specific immunization guidelines, the recommendations given here are often the expression of a consensus derived from descriptive studies, clinical experience and expert opinion (Table 9). They are therefore likely to evolve as new data emerge. Available evidence was obtained from published peer-reviewed studies and from studies presented at international conferences in the last 5 years. In addition, the following websites were consulted: the Health Protection Agency (HPA; www.hpa.org.uk); the USA Centers for Disease Control and Prevention (CDC; www.cdc.gov); and the World Health Organization (WHO; www.who.int/en). The guidelines are generally consistent with and expand the recommendations issued in *The Green Book*, published by the Department of Health, the Scottish Executive, the Welsh Assembly Government and the Department of Health, Social Services and Public Safety, which should be seen as complementary guidance [1].

Table 6 Schedule for pre-exposure vaccination in HIV-infected adults

Vaccine	Indication	Primary course	Boosting	CD4 count (cells/μL)	Comments
Anthrax	RS	Four doses	Yearly	Any	
Cholera (WC/rBS)	RS	Two doses	2 years	Any	
Hepatitis A	RS	Two or three doses	5 years	Any	Three doses if CD4 count <300 cells/μL
Hepatitis B	R	Three or four doses	HBsAb <10 and ideally <100 IU/L	Any	HBsAb levels yearly
Haemophilus influenzae (Hib)	RS	Single dose	None	Any	
Influenza-parenteral	R	Single dose	Repeat yearly	Any	
Japanese encephalitis	RS	Three or four doses	3 years	Any	Four doses if aged >60
Measles, mumps, rubella (MMR)	RS	One or two doses	None	>200	Two doses if measles IgG negative
Meningococcus (MenC)	RS	One or two doses	None	Any	Two doses if asplenia or splenic dysfunction
Meningococcus (ACWY)	RS	Single dose	5 years	Any	
Pneumococcus (PPV23)	R	Single dose	Generally none	Any	Consider boosting after 5–10 years
Rabies	RS	Three doses	1 year (first); 3–5 years (subsequent)	Any	
Tetanus-diphtheria/parenteral poliomyelitis (Td/IPV)	R	One to five doses	10 years	Any	
Tick-borne encephalitis	RS	Three or four doses	3 years	Any	Four doses if CD4 count <400 cells/μL
Typhoid (ViCPS)	RS	Single dose	2–3 years	Any	Boosting after 2 years if CD4 count <200 cells/μL
Varicella	RS/CS	Two doses	None	$>400/>200$	
Yellow fever	CS	Single dose	10 years	>200	Contraindicated if aged >60

C, consider; CS, consider in selected persons; HBsAb, serum surface antibody; R, recommended; RS, recommended in selected persons.

Table 7 Vaccines for travel-related indications

Vaccine	Indication	Comments	CD4 count (cells/μL)
Meningococcus (ACWY)	M	Recommended for travel to endemic or epidemic areas; mandatory for all Hajj and Umrah pilgrims; follow standard guidelines	Any
Yellow fever	M	Consider if at true risk of infection	>200
Hepatitis B	R	If prolonged travel	Any
Measles, mumps, rubella (MMR)	R	If measles IgG seronegative	>200
Tetanus-diphtheria/ parenteral poliomyelitis (Td/IPV)	R	Every 10 years	Any
Cholera (WC/rBS)	S	Follow standard guidelines	Any
Hepatitis A	S	Follow standard guidelines	Any
Japanese encephalitis	S	Follow standard guidelines	Any
Tick-borne encephalitis	S	Follow standard guidelines	Any
Typhoid (ViCPS)	S	Low threshold for offering vaccination	Any
Rabies	S	Low threshold for offering vaccination	Any

M, mandatory for travel to selected countries. These vaccines are legal requirements for travel to some countries. Failure to obtain the vaccine could result in non-entry/quarantine in destination. Waiver documents may not be accepted by some countries.
R, recommended.
S, vaccine for selective use for travellers to risk areas. Recommendations for these vaccines depend on the countries of destination, the epidemic situation at the time of travel, the purpose of travel, the intended length of stay and the health status of the traveller. Because recommendations will change from time to time, it is prudent to access up-to-date health information for specific destinations; this is available from the CDC (www.cdc.gov/travel/default.aspx) and WHO (www.who.int/ith/en/).

It is recognized that the responsibility for providing the recommended immunizations and for meeting the associated costs remains an unresolved issue. It is currently envisaged that the HIV specialist should provide overall guidance on vaccine use and enlist the help of primary care physicians for vaccine administration where feasible. As is the case with HIV-negative travellers, HIV-infected persons should be advised that they will be expected to meet the cost of vaccines required for travel. Finally, while it is hoped that these guidelines will inform immunization practices widely, they are intended primarily for HIV-infected adults in the UK.

1.1 General principles of immunization in HIV-infected adults

- Persons with symptomatic HIV infection or CD4 counts <200 cells/μL must not be given live vaccines. If indicated, vaccination should be reconsidered following immunoreconstitution.
- Household and other close contacts of severely immunocompromised HIV-infected persons should not receive the oral polio and the intranasal influenza vaccines, but can receive the MMR, varicella and yellow fever vaccines.
- Asymptomatic HIV-infected persons with CD4 counts >400 to 500 cells/μL are generally regarded as sufficiently immunocompetent, whereas those with CD4 counts between 200 and 400–500 cells/μL are consid-

Table 8 Post-exposure prophylaxis for HIV-infected adults

Disease	Recommendations	Timing
Anthrax	Antibiotic prophylaxis ± vaccine	As soon as possible
Diphtheria	Antibiotic prophylaxis and tetanus-diphtheria/parenteral poliovirus vaccine (Td/IPV)	As soon as possible
Hepatitis A	If susceptible, vaccine and human normal immunoglobulin (HNIG)	Within 14 days and up to 28 days
Hepatitis B	Previously unvaccinated: vaccine and hepatitis B immunoglobulin (HBIg)	Within 2 days and up to 7 days
	Previously vaccinated with surface antibody (HBsAb) response <10 IU/L: one booster dose + HBIg	May be considered up to 6 weeks
	Previously vaccinated with HBsAb response >10 IU/L: one booster dose; add HBIg if CD4 count <200 cells/μL	
Haemophilus influenzae	Antibiotic prophylaxis	As soon as possible
Influenza	Consider chemoprophylaxis	
Measles	HNIG	Within 6 days
Meningococcus	Antibiotic prophylaxis and vaccine if in contact with group ACW or Y	As soon as possible
Pertussis	Antibiotic prophylaxis	Within 21 days
Poliomyelitis	HNIG unless known to be seropositive for all three polio types	As soon as possible
Rabies	Vaccine ± human rabies immunoglobulin (HRIG)	
Tetanus	Td vaccine ± tetanus immunoglobulin (TIG)	
Varicella	CD4 count <400 cells/μL: varicella-zoster immunoglobulin (VZIG) ± aciclovir	Within 7 days and up to 10 days
	CD4 count >400 cells/μL: consider vaccine	From 7–10 days after exposure for 7 days Within 3 days

Table 9 Level of evidence and grading of recommendations

Level of evidence	
Ia	Meta-analysis of randomized controlled trials
Ib	At least one randomized controlled trial
IIa	At least one well-designed controlled study without randomization
IIb	At least one other type of well-designed quasi-experimental study
III	Well-designed non-experimental descriptive studies
IV	Expert committee reports or opinions of respected authorities
Grading of recommendation	
A	Evidence at level Ia or Ib
B	Evidence at level IIa, IIb or III
C	Evidence at level IV

ered to have limited immunodeficiency. While acknowledging that treated persons with previous symptomatic disease and low nadir CD4 cell counts may have incomplete immunoreconstitution, it is generally recommended that the current CD4 cell count can be used to categorize HIV-infected persons. When safety concerns restrict vaccine use according to the level of immunoreconstitution, it is recommended that the CD4 cell count has been stably above the threshold for at least 3 months before proceeding with vaccination. In all cases, the immunocompetence of individual patients should be judged clinically.

- Regardless of the CD4 cell count, the contraindications to the use of live vaccines that apply to the general population also apply to HIV-infected persons. For further details the reader should refer to *The Green Book* [1]. Risk groups include patients in the following categories:
  - Currently being treated for malignant disease with immunosuppressive chemotherapy or radiotherapy, or have terminated such treatment within the previous 6 months;
  - Have received a solid organ transplant and are currently on immunosuppressive treatment;
  - Have received a stem-cell transplant, until at least 12 months after finishing all immunosuppressive treatment (or longer where the patient has developed graft-*vs.*-host disease);
  - Receiving systemic steroids until at least 3 months after treatment has stopped (in the general population, the threshold is at least 40 mg of prednisolone per day for more than 1 week; lower doses may be associated with significant immunosuppression in HIV-infected persons);
  - Receiving other types of immunosuppressive drugs (e.g. azathioprine, cyclosporin, methotrexate, cyclophosphamide, leflunomide or the newer cytokine inhibitors) alone or in combination with lower doses of steroids, until at least 6 months after terminating such treatment.
- In vaccine candidates with CD4 counts <200 cells/μL, consideration may be given to delaying immunization until the CD4 cell count has recovered with HAART. Because responses to vaccination can be observed in a substantial proportion of patients with CD4 counts <200 cells/μL, the potential benefit of immunization should not be denied to such persons. Therefore, it is generally recommended that vaccination should be given to persons with CD4 counts <200 cells/μL if indicated and safe, and repeated following immunoreconstitution if required.
- Considerations on destination and risk behaviour apply equally to HIV-positive and HIV-negative travellers.

However, the consequences of not administering an indicated vaccine may be more severe in HIV-infected persons. Modification of the travel itinerary may be required where a vaccine is contraindicated in an HIV-infected person, if the risk of infection is significant.

- HIV-infected vaccine recipients should be advised that the levels and duration of protection induced by vaccination may be reduced relative to healthy individuals. The importance of additional measures of protection (e.g. against insect bites) should be emphasized.
- Transient increases in plasma HIV RNA load have been reported after the administration of several vaccines. Available evidence indicates that the transient increases do not have clinical significance [2,3]. These effects will not be discussed further because they should not preclude the use of any vaccine.

1.2 Practical aspects of immunization and general contraindication

For these, the reader should refer to *The Green Book* [1]. In general:

- Live vaccines can be administered simultaneously in different sites or with an interval of 4 weeks. When multiple vaccines are given at the same time a separate site should be used. If the vaccines are given in the same limb, they should be given at least 2.5 cm apart.
- Live vaccines should be administered at least 14 days before or 3 months after the administration of antibody-containing blood products, because passively acquired antibodies may interfere with the response to the vaccine.
- As a general rule, vaccines are contraindicated in persons with a history of previous severe adverse reaction or allergy to the vaccine or its components. In addition, persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated.
- Inactivated vaccines may be used in pregnancy if there is a significant risk of infection. Live vaccines are instead contraindicated in pregnancy, although in most cases the theoretical risk to the developing foetus is expected to be low. The reader should seek specialist advice about vaccination in pregnancy [1].

2.0 Anthrax

2.1 Background

Bacillus anthracis is a toxin-producing gram-positive bacterium transmitted through spores that can be found in animal products and can remain viable in the environment for years. The infection occurs primarily in herbivorous mammals. Human infection is rare and occurs almost exclusively after contact with infected animals or animal products. Person-to-person transmission may occur through contact with skin lesions but is unusual.

The incubation period of anthrax is usually 1–7 days, but can range up to 8 weeks. The disease may present as one of three main syndromes: cutaneous, following direct contact with spores, spore-contaminated material or infected skin lesions (>95% of cases, rare mortality); respiratory, following inhalation of spores (50% mortality); and gastrointestinal, following ingestion of contaminated meat (very rare, 25–60% mortality). Meningitis may occur and is usually fatal. Provided it is recognized early, anthrax can be treated effectively with antibiotics. Post-exposure prophylaxis can also prevent disease if given early enough.

2.2 Epidemiology and risk groups

Anthrax occurs in Asia, Africa and parts of Europe and the Americas. In the UK, human anthrax is rare and is seen almost entirely as an occupational disease in persons handling imported animal products or working with infected animals. Cases have been reported in abattoir workers, tannery/leather workers, farm workers, butchers, engineers, textile workers and bone meal workers.

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

2.3 Anthrax vaccine

The anthrax vaccine is inactivated. It contains alum-precipitated antigen derived from the Sterne strain of *B. anthracis*. In the UK, the only licensed vaccine is manufactured by the HPA and supplied to the Department of Health for occupational health purposes and to the Ministry of Defence to protect service personnel from the use of anthrax as a biological weapon [1]. The vaccine is given by intramuscular injection (or subcutaneously in persons with bleeding disorders), preferably in the deltoid.

2.3.1 Vaccine efficacy

There have been no formal efficacy trials with the UK vaccine and no data are available on vaccine efficacy in HIV-infected persons.

2.3.2 Vaccine safety

The vaccine is safe [4]. It may cause mild injection site reactions and (more rarely) lymphadenopathy, fever, flu-like symptoms, rash, itching or other allergic reactions.

2.4 Recommendations for anthrax pre-exposure prophylaxis in HIV-infected adults

- The anthrax vaccine is indicated in those with a significant risk of exposure [C, IV (see Table 9 for definitions of evidence levels)].
- The primary course consists of four doses. The second dose is given at least 3 weeks after the first, the third dose at least 3 weeks after the second, and the fourth dose at least 6 months after the third (C, IV).
- A single booster dose is given once a year (C, IV).

2.5 Post-exposure prophylaxis

Following credible or confirmed exposure to anthrax, the person at risk should receive post-exposure prophylaxis with oral ciprofloxacin, doxycycline or amoxicillin (if the strain is susceptible) for 60 days and may also be given the vaccine. Immunization is recommended because of the uncertainty of when or if the inhaled spores may germinate. Advice must be obtained from the Immunization Department of the HPA Centre for Infections (tel: + 44 20 8200 6868).

3.0 Cholera

3.1 Background

Vibrio cholerae is a non-invasive toxin-secreting gram-negative bacterium that colonizes the small bowel. Classification into over 100 serogroups is based on the polysaccharides of the somatic (O) antigen. Cholera epidemics are caused by the O1 serogroup, and more recently by the O139 serogroup in south and south-east Asia [5]. The infection is acquired through the faecal–oral route, primarily by consuming contaminated water or food; person-to-person transmission is rare. Mankind is the only known host.

The incubation period of cholera ranges from <1 day to 5 days. The disease is characterized by sudden onset of painless, profuse watery diarrhoea and responds to fluid- and electrolyte-replacement therapy. In extreme cases, hypotension and death can occur within 6–8 h of the onset of symptoms. Approximately 80% of infected people have mild diarrhoea or may be asymptomatic.

3.2 Epidemiology and risk groups

Seven cholera pandemics have been recorded throughout history. The latest started in 1961 and it is still ongoing in regions of Asia, the Middle East, Africa, and central and Latin America, with 3–8 million cases reported each year. Large outbreaks are usually caused by a contaminated water supply. In developed countries, cases are reported sporadically in travellers, with an overall risk of two to three cases per million travellers. Cholera is rare among UK travellers, and is seen predominantly among those who visit the Indian sub-continent. Travellers who follow the usual tourist itineraries, use standard tourist accommodation and observe food safety recommendations while in countries reporting cholera have little risk. The risk increases for long-term travellers and for those who drink untreated water, eat poorly cooked or raw seafood, or live in unsanitary conditions in disease-endemic areas (e.g. aid workers assisting in disaster relief or refugee camps and adventurous backpackers travelling to remote areas) [6]. Currently, no country requires proof of vaccination against cholera as a condition for entry. However, local authorities may require documentation of vaccination.

Persons with underlying gastrointestinal disease or immunodeficiency may be at increased risk for severe disease. Recent findings also suggest that in cholera-endemic areas, HIV infection is associated with an increased risk for cholera [7].

3.3 Cholera vaccine

Several oral cholera vaccines are available internationally. The WC/rBS vaccine available in the UK contains inactivated Inaba and Ogawa strains of *V. cholerae* serotype O1, together with recombinant B-subunit of the cholera toxin produced in Inaba strains of *V. cholerae* serotype O1 [1]. The old parenteral cholera vaccine based on inactivated *V. cholerae* O1 is still produced in some countries but it is not generally recommended because it offers modest and short-lived protection. Production of the live attenuated CVD 103-HgR vaccine has currently been discontinued.

3.3.1 Vaccine efficacy

In healthy persons, the oral cholera vaccines confer 85–90% protection, starting 10 days after the second dose and lasting for at least 1 year [8–10]. The level of protection is approximately 50% after 3 years. Interestingly, there is herd protection of unvaccinated young children whose mothers have received the vaccine [11]. The WC/rBS vaccine is not expected to confer protection against *V. cholerae* O139. WC/rBS (but not CVD 103-HgR) appears to provide some protection against travellers' diarrhoea caused by heat-labile toxin-producing *Escherichia coli* during the first 3 months following vaccination [12]. However, use for the specific prevention of travellers' diarrhoea remains controversial.

There have been no published reports of the efficacy of the WC/rBS vaccine in HIV-infected individuals. A study conducted in Beira, Mozambique, showed promising results

in a population including approximately 25% HIV-seropositive persons (P.A. Parment, personal communication). HIV-infected adults with CD4 counts <100 cells/μL may be expected to respond poorly to oral cholera vaccines, whereas those with CD4 counts >100 cells/μL show improved responses after two doses [13]. Duration of immunity is unknown in HIV-infected persons.

3.3.2 Vaccine safety

The WC/rBS vaccine may cause occasional gastrointestinal symptoms. Fever, malaise, nausea, vomiting, loss of appetite and dizziness have been reported in rare cases. Fatigue, dyspepsia, shivers, joint pain, sore throat, sweating, insomnia and rash are very rare. The vaccine is well tolerated in HIV-infected people.

3.3.3 Contraindications

The vaccine should not be co-administered with other oral vaccines.

3.4 Recommendations for cholera pre-exposure prophylaxis in HIV-infected adults

- Vaccination should be considered for selected HIV-infected persons if they are due to travel to highly endemic areas and fall in one of the risk groups (C, IV). The vaccine is not indicated for most travellers, but should be considered for those who are unable to take adequate precautions in highly endemic or epidemic settings or may be at risk of severe disease if infected.
- HIV-infected persons should receive two doses of the oral WC/rBS vaccine given at least 1 week (usually 10–14 days) apart. If more than 6 weeks have elapsed since the first dose, the course should be recommenced. A single booster dose should be given after 2 years if continued protection is required. If more than 2 years have elapsed since completion of the primary vaccine course, the primary course should be repeated (C, IV).
- The importance of food and water precautions should be emphasized.
- The live attenuated CVD 103-HgR vaccine is contraindicated because of insufficient safety data.

4.0 Diphtheria

4.1 Background

Diphtheria is caused by toxigenic strains of the gram-positive bacteria *Corynebacterium diphtheriae* or *Corynebacterium ulcerans*. The infection is transmitted via airborne droplets, generally as a result of close contact with infectious patients or carriers. Patients with untreated disease may be infectious for up to 4 weeks. Carriers may be asymptomatic and transmit the infection for longer. The normal reservoir of *C. ulcerans* is cattle; rare human cases have been associated with the consumption of raw unpasteurized dairy products. The incubation period of diphtheria is 2–5 days. The disease affects the upper respiratory tract and occasionally the skin. Life-threatening complications include cardiac failure and paralysis.

4.2 Epidemiology and risk groups

In industrialized countries with high vaccine coverage (including the UK), the circulation of *C. diphtheriae* has virtually ceased and there is little risk of exposure [1,14]. Circulation of toxigenic strains of *C. diphtheriae* persist in much of the world and diphtheria cases continue to be reported from the Indian sub-continent, south-east Asia, South America, Africa and recently the Russian federation. The potential for infection and re-introduction into the UK through travel to and emigration from these regions remains a real possibility. Susceptibility to diphtheria increases with age and it is estimated that approximately 50% of UK adults over 30 years of age are susceptible. Travel to endemic countries and close contact with cattle or other farm animals are potential risk factors for infection.

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

4.3 Diphtheria vaccine

The diphtheria vaccine is made from cell-free purified toxin extracted from *C. diphtheriae*, treated with formaldehyde, converted into diphtheria toxoid and adsorbed onto aluminium phosphate or hydroxide. The vaccine is given to adults in combination with tetanus and inactivated polio vaccines in a preparation containing a lower dosage of diphtheria toxoid than preparations designed for use in childhood (Td/IPV) [1]. The vaccine is administered by intramuscular injection (or subcutaneous injection in persons with bleeding disorders), preferably in the deltoid.

4.3.1 Vaccine efficacy

In healthy persons the diphtheria vaccine induces protective antitoxin levels in 95% of individuals after three doses and shows a clinical efficacy of over 97% [1,15]. Adequate anamnestic responses are seen following a booster dose in previously immunized adults [16]. Limited data exist on the

immunogenicity and clinical efficacy of the vaccine in HIV-infected adults. Vaccine responses may be reduced compared to HIV-negative persons [17–19], especially in those with advanced disease and low CD4 cell counts [20,21], but may improve with highly active antiretroviral therapy (HAART) [22].

4.3.2 Vaccine safety

The diphtheria vaccine is safe in HIV-infected persons [17–22]. Injection site reactions are common but usually self-limiting and may occur more frequently following subsequent doses. Fever and other systemic reactions are uncommon. Severe reactions such as generalized urticaria, anaphylaxis or neurological complications have been reported rarely.

4.4 Recommendations for diphtheria pre-exposure prophylaxis in HIV-infected adults

- Vaccination is recommended in all HIV-infected persons regardless of CD4 cell counts and should be given in accordance with standard recommendations.
- A full vaccine course consists of five doses. Adults who have not previously been immunized or have uncertain vaccination status should receive three doses at least 1 month apart. Two further boosting doses should be given after 5 and 10 years. Adults who have received three doses as infants and one booster at pre-school age (total of four doses) require a single booster dose. Persons who have received five doses require a booster dose at 10-yearly intervals if at risk of exposure (C, IV). There is no need to restart a series if more than the recommended time between doses has elapsed.
- Individuals who may be exposed to diphtheria in the course of their work (e.g. laboratory workers) should be tested for antibodies 3 months after vaccination to confirm protective immunity.

4.5 Post-exposure prophylaxis

Individuals who are close contacts of a case of diphtheria should receive vaccination and antibiotic prophylaxis as soon as possible [23]. Unimmunized individuals should receive three doses of Td/IPV. Previously immunized individuals should receive a single booster dose of Td/IPV, unless a booster dose was given within the past year. The recommended regimen for antibiotic prophylaxis for adults is a single dose of intramuscular benzyl penicillin (1.2 M units) or erythromycin 500 mg every 6 h for 7 days.

4.6 Auditable outcomes

Documented completion of primary vaccination (target 75%).

5.0 *Haemophilus influenzae* serotype b

5.1 Background

Haemophilus influenzae is a gram-negative coccobacillus transmitted through contact with respiratory droplets. Serious infection is usually caused by strains carrying a polysaccharide capsule. Six typeable capsular serotypes have been identified (a–f). Secondary *H. influenzae* disease is defined as illness occurring 1–60 days following contact with an ill person. The most important manifestations of disease – meningitis and pneumonia – usually occur in children below the age of 5 years. Other manifestations are epiglottitis, bacteraemia, arthritis, cellulitis, osteomyelitis and pericarditis. In the pre-vaccine era, 95% of cases of invasive disease were associated with *H. influenzae* serotype b (Hib). Hib can also colonize the nasopharynx in the absence of symptoms. Non-typeable (non-capsulated) strains of *H. influenzae* are a rare cause of invasive disease among children, but are a common cause of ear infections in children and bronchitis in adults.

5.2 Epidemiology and risk groups

H. influenzae remains a leading cause of disease and mortality in children in developing countries. In developed countries, routine vaccination in children has led to a dramatic reduction in invasive disease. Some older children and adults with underlying conditions are at increased risk of disease. These include:

- absent or non-functioning spleen (e.g. sickle cell disease);
- antibody deficiency syndromes (especially IgG2 subclass deficiency);
- other immunodeficiency caused by disease or treatment, including HIV infection.

The risk of infection is increased in HIV-seropositive adults compared to the general population [24,25]. In one study, the cumulative incidences of invasive *H. influenzae* disease in men aged 20–49 years with HIV infection or AIDS were 14.6 and 79.2 per 100 000, respectively. Only 33% of cases were caused by Hib [24].

5.3 Hib vaccine

The Hib vaccines are protein-polysaccharide conjugates. Vaccines available in the UK are conjugated with either

CRM197 (a non-toxic variant of diphtheria toxin) or tetanus toxoid [1]. The vaccine is used either as combined diphtheria/tetanus/acellular pertussis/inactivated polio/Hib (DTaP/IPV/Hib) or as a single Hib vaccine. The vaccine is given by intramuscular injection (or subcutaneous injection in persons with bleeding disorders), preferably in the deltoid.

5.3.1 Vaccine efficacy

The Hib vaccine is highly immunogenic in healthy infants. More than 95% develop protective antibody levels after a primary series of two or three doses and clinical efficacy is 95–100%. The duration of protection is unknown. No booster doses are currently recommended for healthy persons. The vaccine is immunogenic in patients with HIV infection. However, immunogenicity varies with stage of infection and degree of immunodeficiency [26–31]. There are no data on clinical efficacy of vaccination in this population.

5.3.2 Vaccine safety

Injection site reactions, including swelling, redness or pain, have been reported in 5–30% of recipients and these usually resolve within 12–24 h. They are more common when the vaccine is given subcutaneously. Systemic reactions such as fever and irritability are infrequent. Anaphylaxis and other serious adverse reactions are rare. No safety concerns have emerged in individuals with HIV infection.

5.4 Recommendations for *H. influenzae* pre-exposure prophylaxis in HIV-infected adults

- Vaccination is not routinely recommended in HIV-infected adults. However, where HIV-infected adults are scheduled to receive other vaccines, a multivalent vaccine including Hib may be considered (C, IV). A single vaccine dose is recommended in adults.
- HIV-infected adults who acquire splenic dysfunction should receive one Hib vaccine dose, whether or not they were immunized in infancy.
- HIV-infected adults who have recovered from Hib disease and have risk factors for further disease, those with recurrent pulmonary infections or other risk factors for severe disease should be considered for vaccination with one Hib dose (C, IV).

5.5 Post-exposure prophylaxis

HIV-infected persons who are household contacts of a Hib case should be given rifampicin prophylaxis, regardless of their immunization status. The recommended dose is 20 mg/kg/day (up to a maximum of 600 mg daily) once daily for 4 days. Patients on highly active antiretroviral therapy (HAART) may take ciprofloxacin as an alternative to rifampicin. HIV-infected contacts of a case of invasive Hib disease should be offered one vaccine dose.

5.6 Auditable outcomes

HIV-infected persons who acquire splenic dysfunction should receive one Hib vaccine dose (target 95%).

6.0 Hepatitis A

6.1 Background

The hepatitis A virus (HAV) is a Picornavirus transmitted faeco-orally through close personal contact, contaminated food and water, and rarely through blood exposure. Person-to-person spread is the most common method of transmission in developed countries. There is evidence that the infection may be spread during sexual contact in homosexual men [32].

The incubation period of hepatitis A is usually 28 days (range 15–50 days). Infection may be asymptomatic, but severity tends to increase with age. Jaundice occurs in $<10\%$ of children below the age of 6 years, 40–50% of older children and 70–80% of adults. Recovery normally occurs in 2–6 weeks. Fulminant hepatitis occurs rarely ($<1\%$ overall) but carries $>50\%$ risk of mortality. Although approximately 15% of infected persons show prolonged or relapsing symptoms over 6–9 months, chronic infection is not known to occur. Infection is followed by lifelong immunity.

6.2 Epidemiology and risk groups

HAV prevalence is low in northern and western Europe, North America, Australia, New Zealand and Japan, and intermediate to high in Mexico, Central and South America, the Caribbean, Africa, Asia and Eastern Europe.

Those at risk for infection include the following:

- household and sexual contacts of infected persons;
- travellers to countries where HAV is common;
- men who have sex with men;
- injecting and non-injecting drug users;
- individuals at risk of infection during outbreaks;
- those with occupational exposure to HAV (e.g. laboratory workers, sewage workers);
- persons with haemophilia;

- persons with special needs living in residential institutions and their carers.

Patients with chronic liver disease and chronic infection with hepatitis B or hepatitis C are at risk of severe complications [33,34].

Hepatitis A does not appear to be worse in HIV-infected patients when compared to HIV-negative persons [35], although HAV viraemia may be prolonged [36,37].

6.3 Hepatitis A vaccine

The HAV vaccine contains formaldehyde-inactivated virus grown in human diploid cells. There are also combined hepatitis A/hepatitis B and hepatitis A/typhoid vaccines. The HAV vaccine is given intramuscularly (or subcutaneously in persons with bleeding disorders), preferably in the deltoid [1].

6.3.1 Vaccine efficacy

In healthy persons, the HAV vaccine is highly immunogenic and efficacious. Protective levels of antibodies develop in 97–100% of individuals within 1 month of the first dose and in virtually 100% after the second dose. The level of protection against clinical hepatitis is 79–100% after a single dose. The combined hepatitis A/hepatitis B vaccine is also highly efficacious [1]. Successful immunization in healthy persons is thought to confer protection for over 10 years; current opinion suggests that immunity may be lifelong.

Response rates are generally reduced in HIV-infected persons compared to HIV-negative persons, and correlate with the CD4 cell count at the time of vaccination [38–46]. Rates are 50–95% overall, but range from 9% at CD4 counts <200 cells/μL to 95–100% at CD4 counts >300–500 cells/μL. Plasma HIV RNA suppression on highly active antiretroviral therapy (HAART) is associated with improved anti-HAV antibody levels [22]. Increasing the number of doses may also improve responses [40]. Duration of protection in HIV-infected people is unknown, but may be shorter than in HIV-negative persons.

6.3.2 Vaccine safety

The HAV vaccine is safe and well tolerated in HIV-infected individuals [39,40]. Injection site reactions are the most frequent side effects. Malaise and headache for 1 or 2 days may occur occasionally. Serious allergic reactions are very rare.

6.4 Human normal immunoglobulin

Human normal immunoglobulin (HNIG) is 80–90% effective in preventing clinical hepatitis for 3–6 months but is no longer indicated for pre-exposure prophylaxis. Current preparations vary in the levels of HAV antibodies and commercial supplies can no longer be relied upon to provide protection. Effective preparations are available through the HPA (or can be bought from the Scottish National Blood Transfusion Service) but supplies are only available for limited indications.

HNIG causes minor local reactions and may cause an influenza-like illness and (rarely) anaphylaxis. It is contraindicated in those with a previous severe reaction. When indicated, the HAV vaccine and HNIG can be given together (using a different site) intramuscularly (or subcutaneously in persons with bleeding disorders), preferably in the deltoid.

6.5 Recommendations for hepatitis A pre-exposure prophylaxis in HIV-infected adults

- Vaccination is recommended in all HIV-positive persons that belong to a group at risk for the infection or its complications (C, IV).
- HIV-infected persons with CD4 counts >300 cells/μL may follow the standard vaccination schedule and receive two doses at 0 and 6–12 months (B, IIa).
- HIV-infected persons with CD4 counts <300 cells/μL should receive three doses over 6–12 months (B, IIa).
- The combined hepatitis A/hepatitis B vaccine is given at 0, 1 and 6 months.
- HIV-infected persons at risk for the infection should receive a boosting dose every 5 years (C, IV).
- The HAV vaccine is recommended for HIV-infected travellers to areas of high or intermediate endemicity. It should be given at least 2 weeks before travel. In people at very high risk of hepatitis A and its complications who have a CD4 count <200 cells/μL, HNIG (500 mg) may be considered together with the vaccine before travel (C, IV).
- Vaccination of a person who is immune because of prior infection does not increase the risk of adverse events. Pre-vaccination testing for HAV-specific IgG (or total anti-HAV) may be considered if shown to be cost-effective in a specific clinical setting. This may be routine screening of all vaccine candidates or targeted screening of those who were born in or lived for extensive periods in geographic areas that have a high-to-intermediate endemicity of HAV infection, homo-

sexual males, injecting drug users and persons above the age of 50 years (C, IV).
- Routine post-vaccination testing is not generally recommended, but may be considered in selected high-risk individuals (C, IV).

6.6 Post-exposure prophylaxis

Post-exposure prophylaxis of susceptible persons with HAV vaccine and HNIG (500 mg) given within 14 days of exposure can prevent or attenuate disease following a high-risk contact (e.g. in the household setting or other intimate contact). Efficacy beyond 14 days of exposure is unknown; disease may be attenuated rather than prevented. In HIV-negative people the efficacy of post-exposure prophylaxis is determined by the interval between exposure and administration and is in the range 47–87%. There are no data on the efficacy of post-exposure prophylaxis in HIV-infected people. Although early vaccination alone without HNIG seems to be effective in HIV-negative people, there are no data for HIV-infected persons.

6.7 Recommendations for hepatitis A post-exposure prophylaxis in HIV-infected adults

- Following a high-risk exposure to HAV, the hepatitis A serostatus should be determined by measuring HAV IgG or total antibodies. Post-exposure prophylaxis with HAV vaccine and HNIG (500 mg) is recommended in all HAV seronegative HIV-infected persons (C, IV). Administration should be as soon as possible and not delayed by waiting for the serology results.
- Prophylaxis should be given within 14 days of exposure, but may be considered up to day 28 (C, IV).

6.8 Auditable outcomes

(1) Offer hepatitis A vaccination to HIV-infected persons who are at increased risk of the disease or its complications, within 6 months of HIV diagnosis (target 95%).
(2) Complete the vaccination course within 12 months (target 90%).

7.0 Hepatitis B

7.1 Background

The hepatitis B virus (HBV) is transmitted through sexual intercourse, percutaneous and parenteral exposure to blood and infected body fluids, and vertically from mother to child. The incubation period of hepatitis B is usually 90 days (range 40–160 days). The severity of acute infection varies from asymptomatic to fulminant hepatitis. After primary infection, HBV persists in 90% of infants infected perinatally, 25–50% of children aged 1–5 years and 1–5% of immunocompetent adults and older children. Chronic infection can lead to chronic liver disease, cirrhosis and hepatocellular carcinoma.

7.2 Epidemiology and risk groups

Based on the prevalence of the infection, three geographical categories can be identified: low prevalence (<2%), intermediate prevalence (2–8%) and high prevalence (>8%). Regions of low prevalence include western, northern and central Europe, Australia and North America. Worldwide, the risk of infection is increased in injecting drug users, homosexual males, those with multiple sexual partners, household and other close contacts of HBV-infected persons, those receiving regular blood or blood products, patients and staff of haemodialysis centres, people sharing unsterile medical and dental equipment, people providing and receiving acupuncture and tattooing with unsterile devices, healthcare workers, staff and residents of residential accommodation for those with mental disabilities, and travellers to areas of high prevalence [1].

Both the risk of HBV infection and that of chronicity are increased in HIV-seropositive persons [47]. Chronic HBV infection is found in 6–10% of HIV-infected persons in the UK [48] and co-infected persons show increased risk of progression to cirrhosis and liver cancer, with a 25–30% lifetime risk for either complication. The mortality rate of HIV/HBV co-infected patients is approximately 10 times higher than that seen in persons with either infection alone [48].

7.3 Hepatitis B vaccine

The HBV vaccine is prepared with biosynthetic surface antigen made using recombinant technology. There is also a combined hepatitis A/hepatitis B vaccine. The vaccine is given intramuscularly (or subcutaneously in persons with bleeding disorders), preferably in the deltoid. The buttock must not be used: it may cause reduced vaccine efficacy.

7.3.1 Vaccine efficacy

The traditional vaccine schedule consists of three doses given at 0, 1 and 6 months. The accelerated vaccine schedule consists of three doses given at 0, 1 and 2 months followed by an additional dose at 12 months. The two schedules show similar efficacy in HIV-infected persons

[49,50]. The ultra-rapid vaccination schedule consists of three doses given at 0, 7–10 days and 21 days, with an additional dose at 12 months [51]. There is very limited evidence on the efficacy of the ultra-rapid schedule in HIV-infected persons [52], but controlled trials are under way.

In healthy persons, 80–90% of vaccinated young adults achieve serum surface antibody (HBsAb) levels >10 IU/L. Antibody levels >100 IU/L are regarded as ideal whereas a level <10 IU/L is classified as non-response [53,54]. The combined hepatitis A/hepatitis B vaccine is also highly efficacious. Factors that reduce responses include age above 40 years, obesity, female gender, haemodialysis and smoking. The duration of HBsAb persistence is not known precisely. Successful immunization in healthy adults prevents disease for over 10 years and current opinion suggests that immunity may be lifelong [55]. There is some evidence that protective immunity is still present even though HBsAb levels have fallen <10 IU/L. Infection in vaccinees may occur, but this is mostly transient and subclinical [56,57]. There is currently a lack of consensus on the requirement for booster vaccine doses in successfully vaccinated healthy individuals. Current guidelines recommend that healthy persons receive a single booster dose given 5 years after completion of the primary vaccine course if they continue to be at risk of infection.

Response rates and HBsAb levels and durability are reduced in HIV-positive people [58–60]. Response rates range between 7 and 88% and correlate strongly with CD4 cell count, CD4 cell count nadir and plasma HIV RNA load [49,50,61–68]. Rates of achieving HBsAb levels >10 IU/L after standard vaccination are 56–88% at CD4 count >500 cells/μL, but only 25% or less with CD4 counts <350–200 cells/μL. Elevated levels of CD8 + /CD38 + /HLA–DR + T-cells predict reduced responses, providing a rationale for the observed effect of ongoing viral replication on responses to vaccination [64]. Nonetheless, HBV vaccination significantly reduces the risk of incident HBV infection in HIV-infected persons [69]. Although infection can occur in HIV-infected patients who respond to vaccination, it is usually characterized by a mild course and reduced risk of chronicity.

Patients on highly active antiretroviral therapy (HAART) generally show improved responses to HBV vaccination [67]. Strategies to improve responses include revaccination of non-responders once the CD4 count is >500 cells/μL and the plasma HIV RNA is suppressed, and the use of larger or more frequent HBV vaccine doses [50,68,70]. In patients with CD4 counts <500 cells/μL, six vaccine doses given at 0, 1, 2, 3, 4 and 5 months induce HBsAb >10 IU/L in 92% of vaccine recipients [50]. Double-dose vaccination at 0, 1 and 6 months induces HBsAb >10 IU/L in 64% of vaccinees compared to 39% of those receiving the standard dose [68]. In another study, HIV-infected patients who did not develop HBsAb after three vaccine doses were revaccinated with three double doses given at 0, 1 and 2 months beginning a median of 5 weeks after completion of the initial vaccination [70]. Overall, 51% developed an adequate antibody response (HBsAb ≥ 10 IU/L). Revaccination was well tolerated, with no adverse effects. Duration of protection is unknown in HIV-infected persons, but in general terms post-vaccination HBsAb levels are lower and disappear more quickly than in HIV-negative persons. Boosting requirements are not well defined for immunocompromised patients.

The management of persons who are HBsAg-negative, HBcAb-positive and HBsAb-negative is controversial. These patients may belong to one of the following four groups: (i) recent resolving HBV infection (HBV core IgM positive); (ii) occult HBV infection (HBV DNA intermittently positive); (iii) resolved HBV infection (strong HBcAb reactivity, anamnestic HBsAb response >10 IU/L observed 1–2 weeks after a single vaccine dose); (iv) false-positive HBcAb result and susceptibility to infection. HBV vaccination may be considered in these patients.

7.3.2 Vaccine safety

The HBV vaccine is safe and well tolerated in HIV-infected individuals [60]. Injection site reactions are the most frequent side effects. Other reactions may occasionally include fever, rash, malaise, influenza-like symptoms, arthritis, arthralgia, and myalgia. Serious allergic reactions are very rare. The hypothesis that HBV vaccination is a risk factor for multiple sclerosis has been explored extensively but evidence for a causal relationship has not been found. No significant adverse clinical reactions to HBV vaccination distinctive to HIV-infected persons have been reported.

In healthy persons, HBV vaccination induces a transient decrease in T-cell proliferative responses lasting 8 days after the first dose and 4 days after the second dose [71]. It has been proposed that HBV vaccination may temporarily impair the immune response to HBV infection in HIV-infected persons, thus increasing the risk of chronicity should infection occur in the few days immediately after vaccination [72]. The clinical implications of these observations are unclear, but they should not be a deterrent to offering vaccination to HIV-infected persons.

7.4 Recommendations for hepatitis B pre-exposure prophylaxis in HIV-infected adults

- All HIV-infected adults should be screened for evidence of a current or past HBV infection. Screening protocols

may vary, but generally a current infection is diagnosed by testing for HBV surface antigen (HBsAg). In those who are HBsAg-negative, a past infection and natural immunity is indicated by the presence of HBV core antibodies (HBcAb) and HBsAb or HBV e antibodies (HBeAb). No vaccination is required in these cases.

- Vaccination against HBV is recommended in all non-immune HIV-positive persons (B, IIb).
- Based on available evidence, both the standard (0, 1 and 6 months) and rapid (0, 1, 2 and 12 months) schedules can be recommended. Pending further evidence, the ultra-rapid schedule (0, 7–10 and 21 days) may only be considered in selected patients with good immune status (C, IV).
- Intradermal vaccination results in reduced response rates and is not generally recommended (C, IV).
- The HBsAb level should be measured 6–8 weeks after vaccination. Vaccine recipients with HBsAb <10 IU/L should be offered three further double-doses, given at monthly intervals (B, IIa). Depending on the level of risk, revaccination may be delayed until the CD4 count has risen >500 cells/μL on HAART (B, IIa). Retesting for HBsAb is recommended 6–8 weeks after the final vaccine dose (C, IV).
- Vaccine recipients with an HBsAb response >10 but <100 IU/L should be offered one additional vaccine dose. Responses should be rechecked 6–8 weeks later (C, IV).
- Following successful immunization, the HBsAb level should be measured yearly. A booster should be offered to persons whose HBsAb levels have declined <10 and ideally <100 IU/L (C, IV).
- The management of persons who are HBsAg-negative, HBcAb-positive and HBsAb-negative is controversial. They may be offered one vaccine dose, tested for HBsAb 2 weeks later and offered two further doses if the HBsAb level remains <10 IU/L [73] (B, IIa). Routine testing for HBV DNA to diagnose an occult infection is not recommended because HBV DNA detection is intermittent [74].
- HBV vaccination rates are closely dependent on the clinical setting providing HIV care [67], indicating that compliance should be audited regularly.

7.5 Post-exposure prophylaxis

Hepatitis-B-specific immunoglobulin (HBIg) can protect from infection or attenuate disease if given immediately after exposure to HBV, when it is usually combined with the HBV vaccine [75]. Among HIV-negative people, only 1% develop disease and 2% have evidence of infection if prophylaxis is given within 7 days of exposure [76]. Efficacy beyond 7 days is unknown. HBIg affords protection for 3–6 months [1]. A rapid vaccination course started within 7 days of exposure appears to be as effective as vaccination plus HBIg in healthy persons [75]. There are no data on the efficacy of post-exposure prophylaxis by either strategy in HIV-infected persons. HBIg is available from the HPA. It is given by intramuscular injection. When given with the HBV vaccine, a different injection site should be used. Minor local reactions can occur at the injection site. Rarely, anaphylaxis has been observed.

7.6 Recommendations for hepatitis B post-exposure prophylaxis in HIV-infected adults

- Following a high-risk exposure, the HBV immune status should be determined if unknown. Testing should not delay the start of post-exposure prophylaxis.
- No prophylaxis is required in those with evidence of a past HBV infection.
- Persons who have responded to previous vaccination with HBsAb >10 IU/L should be offered a booster dose of the vaccine (C, IV). If the immune status has deteriorated (CD4 counts <200 cells/μL) since the recorded response to vaccination, HBIg should also be given (C, IV).
- Non-responders to previous vaccination (HBsAb <10 IU/L) should be offered a booster dose of the vaccine and HBIg (C, IV).
- Those who have not been vaccinated previously should be offered a rapid course of vaccination (0, 1 and 2 months) and HBIg (C, IV).
- When indicated, two doses of HBIg (500 IU) should be given, 1 month apart (C, IV).
- Those with isolated HBcAb positivity ($HBsAg^-$, $HBcAb^+$, $HBsAb^-$) should be offered one vaccine dose, tested for HBsAb 2 weeks later and offered two further doses if the HBsAb level is <10 IU/L (B, IIa).
- Post-exposure prophylaxis should be given preferably within 2 days and up to 7 days after exposure. Prophylaxis beyond 7 days and up to 6 weeks after exposure may be considered; specialist advice should be sought (C, IV).

7.7 Auditable outcomes

1. Test newly diagnosed HIV-infected patients for hepatitis B infection and immunity within 3 months of HIV diagnosis (target 95%).
2. Offer hepatitis B vaccination to HIV-infected patients who are non-immune within 6 months of HIV diagnosis (target 95%).
3. Complete vaccination course (target 95%).

4. Measure post-vaccine HBsAb levels 6–8 weeks after the last vaccine dose (target 90%).

8.0 Influenza

8.1 Background

There are three types of influenza viruses – A, B and C. Influenza A and influenza B account for most cases of the disease. Influenza A viruses are antigenically variable because of changes in the principal surface antigens, haemagglutinin (H) and neuraminidase (N). Minor changes ('antigenic drift') occur progressively from season to season. Major changes ('antigenic shift') result periodically in the emergence of new sub-types that, because populations may have little immunity to them, can cause epidemics or pandemics. Influenza B viruses are subject to antigenic drift but with less frequent changes. Influenza is highly infectious. Transmission occurs through the respiratory tract via both large droplets and small aerosolized particles.

The incubation period of influenza is 2–3 days (range 1–7 days). Disease severity varies from asymptomatic to fatal infections. Influenza can exacerbate underlying medical conditions (e.g. asthma and chronic obstructive pulmonary disease) and lead to serious complications including primary influenza pneumonia and secondary bacterial pneumonia. Epidemics are associated with a large number of excess deaths from cardiopulmonary causes, mainly among the elderly. Rarely, influenza has been associated with encephalopathy, transverse myelitis, myositis, myocarditis, pericarditis and Reye's syndrome.

8.2 Epidemiology and risk groups

Outbreaks of influenza A occur most years. Influenza B causes less extensive outbreaks, usually between outbreaks of influenza A. The influenza season is October–May in the northern hemisphere and April–September in the southern hemisphere. In the tropics, influenza occurs all year round.

The greatest morbidity and risk for complications, hospitalization and death are seen in very young children, the elderly (≥ 65 years) and those with underlying conditions, including chronic respiratory disease, significant cardiovascular disease, chronic renal or liver disease, diabetes mellitus and immunodeficiency. There is limited information concerning the impact of HIV of the natural history of influenza. Evidence suggests an increased risk of complications, impairment of respiratory function with hypoxaemia, prolonged duration of illness and increased rates of hospitalization [77–81]. Data from the pre-highly active antiretroviral therapy (HAART) era indicated substantial excess mortality during influenza seasons [82]. It is currently unknown whether the magnitude of risk has been reduced by the introduction of HAART.

8.3 Influenza vaccine

The influenza vaccine is prepared each year using virus strains or genetic reassortants similar to those considered most likely to be circulating in the forthcoming winter [1]. Current vaccines are trivalent containing two a and one b serotypes. The vaccine is made from highly purified viruses grown in embryonated hens' eggs, chemically inactivated and then further treated and purified. Two types of vaccine are available: 'split virus' vaccines contain virus components prepared by treating whole viruses with organic solvents or detergents and then centrifuging; 'surface antigen' vaccines contain highly purified haemagglutinin and neuraminidase antigens prepared from disrupted virus particles. The vaccines are equivalent in efficacy and adverse reactions. The influenza vaccine is given intramuscularly (or by deep subcutaneous injection in case of bleeding disorders), preferably in the deltoid, as a single dose in adults.

A live attenuated influenza vaccine (LAIV) for intranasal administration has been approved in the USA for use in healthy people.

8.3.1 Vaccine efficacy

In healthy individuals, influenza vaccination gives 70–80% protection against infection with influenza virus strains related to those in the vaccine. Development of protective antibodies occurs about 2 weeks after vaccination and protection lasts for about 1 year. Although responses to vaccination are often reduced in the elderly and those with underlying conditions, vaccination can still protect against severe disease, complications such as bronchopneumonia, hospital admission and mortality. Vaccine-induced antibody responses are lower in HIV-infected persons compared to HIV-negative controls, especially among those with CD4 counts < 200 cells/μL [83–94]. Responses correlate with CD4 cell counts, and improved success rates are expected in patients with HAART-induced immune reconstitution. HIV-infected patients with CD4 counts > 300 cells/μL while on HAART appear to have humoral and cellular responses to influenza vaccination similar to those of healthy controls [95].

Data on the clinical efficacy of influenza vaccination in HIV-infected adults are limited. In patients receiving antiretroviral therapy (ART) with a CD4 count > 200 cells/μL, the estimated efficacy of vaccination against laboratory-confirmed infection ranges between 69% and

100% [96]. Although the protective effect is significantly reduced in patients with CD4 counts <200 cells/μL, protection against severe disease is observed in this population compared to unvaccinated persons. A systematic review and meta-analysis to assess the efficacy of influenza vaccines in HIV-infected persons found a pooled relative risk reduction of 66% [95% confidence interval (CI) 36–82%], but concluded that a reasonable estimate of influenza vaccination effectiveness in HIV-infected patients could not be derived from available data [97].

8.3.2 Vaccine safety

The influenza vaccine is safe and well tolerated in HIV-infected individuals [98]. Injection site reactions are the most frequent side effects. Rare side effects include fever, malaise, myalgia and/or arthralgia (beginning 6–12 h after immunization and lasting up to 48 h) and allergic reactions (most likely because of hypersensitivity to residual egg protein). Guillain–Barré syndrome has been reported very rarely; a causal relationship with vaccination has not been established.

8.3.3 Contraindication

- Severe allergy to eggs.
- Previous Guillain–Barré syndrome within 6 weeks of receiving an influenza vaccine.

8.4 Recommendations for influenza pre-exposure prophylaxis in HIV-infected adults

- Vaccination against influenza is recommended for all HIV-infected adults and is strongly recommended for HIV-infected adults with additional risk factors among the following (A, Ib):
  - chronic respiratory disease, including asthma;
  - significant cardiovascular disease (excluding hypertension only);
  - chronic renal or liver disease;
  - diabetes mellitus;
  - additional immunosuppression because of disease or treatment, including asplenia or splenic dysfunction, chemotherapy and use of oral steroids for more than a month at a dose equivalent to prednisolone 20 mg or more per day, or high-dose long-acting inhaled steroids;
  - age ≥ 65 years;
  - living in nursing homes, residential homes and other long-stay facilities.
- Manufacture of influenza vaccine is complex and is conducted to a tight schedule. Manufacturers may not be able to respond to unexpected demands for vaccine at short notice. It is recommended that clinics and practices order sufficient vaccine for their needs, well in advance of the immunization season (C, IV).
- The vaccine is given as a single dose in adults. In the northern hemisphere, the ideal time for vaccination is October or early November. Depending on the epidemiological circumstances, there is still a potential benefit of vaccination until March (C, IV).
- The intranasal LAIV is not currently recommended for HIV-infected persons. In addition, immunocompromised HIV-infected persons should generally avoid close contact with anyone who has received the live attenuated vaccine within the previous 21 days (C, IV).

8.5 Antiviral therapy for pre- and post-exposure prophylaxis

Antiviral therapy with either oseltamivir (75 mg orally once daily) or zanamivir (10 mg once daily by inhalation with Diskhaler) can be used for the pre- and post-exposure prophylaxis of influenza. Prophylaxis is expected to be 80% effective in preventing severe illness but the efficacy in HIV-infected persons is unknown. The reader should refer to the British National Formulary (BNF) or http://emc.medicines.org.uk for cautions and contraindications on the use of oseltamivir and zanamivir.

8.6 Recommendations for influenza chemoprophylaxis in HIV-infected adults

- Seasonal pre-exposure chemoprophylaxis is not generally recommended (C, IV).
- Pre-exposure chemoprophylaxis may be considered for unvaccinated HIV-infected persons, or vaccinated persons in whom the vaccine is not expected to be effective (CD4 counts <200 cells/μL or poor match between vaccine and circulating influenza strain), under special circumstances (e.g. persons in institutional settings, in intensive care or awaiting transplantation) and when the epidemiological circumstances indicate that exposure is likely (C, IV). Expert advice should be sought.
- Post-exposure chemoprophylaxis with either oseltamivir or zanamivir started within 48 h of a high-risk contact and given for 10 days should be considered in the following groups: (i) unvaccinated persons; (ii) vaccinated persons in whom the vaccine is not expected to be effective (CD4 count <200 cells/μL or poor match between vaccine and circulating influenza strain); (iii)

persons resident in care establishments regardless of vaccination status (C, IV).
- In case of shortage of antivirals, priority for chemoprophylaxis should be given to HIV-infected patients with CD4 counts <200 cells/μL or additional risk factors (C, IV).

8.7 Auditable outcomes

Offer annual influenza vaccination to all HIV-infected persons (target 95%).

9.0 Japanese encephalitis

9.1 Background

The Japanese encephalitis virus (JEV) is a member of the flaviviridae. The infection is transmitted to humans by the bite of *Culex* mosquitoes; person-to-person transmission has not been reported. The incubation period of Japanese encephalitis is 5–15 days. Severity ranges from asymptomatic infection to severe encephalitis with a high risk of mortality. Approximately 0.5% of the infections become clinically apparent. The case–fatality ratio of patients with encephalitis is 25%, and survivors have a 30% risk of permanent neurological sequelae. The elderly may be more susceptible to developing neurological disease. Limited data indicate that infection during the first or second trimesters of pregnancy causes intrauterine infection and miscarriage.

9.2 Epidemiology and risk groups

JEV is the leading cause of viral encephalitis in Asia. The endemic zone stretches from the Indian sub-continent eastwards across Asia and south-east Asia including China, Taiwan, the Philippines, Vietnam, Nepal, India, Sri Lanka, Thailand, Cambodia, Indonesia, Malaysia, Sarawak and northern Australia. Human infections occur predominantly in rural areas, especially where rice growing and pig farming co-exist. Infections occur only occasionally in urban areas. The highest transmission rates occur during and just after wet seasons, when mosquitoes are most active, but seasonal patterns vary both within individual countries and from year to year.

Travellers to rural areas of south-east Asia and the Far East are considered at risk. The disease risk is extremely low, although it is variable according to the season, location and duration of travel, and the activities of the person. The estimated risk in a 1-month period during the transmission season is one per 5000–20 000 per week. The overall risk for most short-term travellers may be one per million. The use of bed nets, insect repellents and protective clothing and avoidance of outdoor activity, especially during twilight periods and in the evening, will reduce the risk further.

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

9.3 JEV vaccine

There are two (unlicensed) vaccines available for use in the UK, both containing the formalin-inactivated Nakayama strain derived from mouse brains. The vaccine must be given on a named-patient basis [1], by deep subcutaneous injection.

9.3.1 Vaccine efficacy

The recommended vaccine schedule is three doses on days 0, 7–14 and 28. An abbreviated schedule of days 0, 7 and 14 has been used in healthy individuals when the longer schedule is impractical or inconvenient because of time constraints. This is not recommended in immunocompromised individuals because of reduced immunogenicity compared to the standard course [99]. Three doses provide protective and sustained levels of neutralizing antibody in virtually 100% of vaccinees. The duration of protection is not known. Neutralizing antibody persists for at least 2 years after a three-dose course. In healthy persons, a booster is recommended after 3 years for those at continued risk.

No studies have been published on antibody responses to JEV vaccination in HIV-infected adults. One study in children showed a reduced response rate and antibody levels after two doses [100]. There are no data on the immunogenicity of three vaccine doses or on the impact of highly active antiretroviral therapy (HAART) on vaccine responses. It should be assumed that patients with CD4 count <400 cells/μL and especially those with CD4 count <200 cells/μL are likely to have reduced response rates. Although HIV-infected persons may have less durable antibody responses, there is insufficient evidence for modifying the boosting requirements [101,102].

9.3.2 Vaccine safety

The JEV vaccine is moderately reactogenic. Injection site reactions occur in 10–20% of vaccine recipients. About 10% experience systemic reactions such as fever, headache, malaise, chills, dizziness, aching muscles, nausea and/or vomiting. Hypersensitivity reactions may occur, are usually mild to moderate, and are more likely to occur in those with a history of allergic conditions such as asthma, allergic rhinitis, drug, food, gelatine or bee-sting allergy.

The rates of serious hypersensitivity reactions are 1–104 per 10 000. Hypersensitivity reactions usually occur within 24–48 h but can be delayed for 7 days after immunization. Vaccinated persons should be monitored for 30 min after vaccination and have ready access to medical care for 10 days after vaccination. Vaccinees should be warned about the possibility of delayed urticaria and angioedema of the head and airway. Neurological adverse events have been reported rarely. Limited data indicate that the pattern of adverse reactions is not modified by HIV infection [99,100].

9.3.3 Contraindication

- Persons with allergic conditions should be advised about the risk of vaccine-related angioedema and generalized urticaria. A risk assessment needs to take into account the likelihood of exposure and the possible adverse effects of the vaccine.
- Anecdotal reports suggest that the JEV vaccine should not be used in individuals who have recovered from acute disseminated encephalomyelitis or Guillain–Barré or who have multiple sclerosis or other demyelinating disorders.

9.4 Recommendations for Japanese encephalitis pre-exposure prophylaxis in HIV-infected adults

- Vaccination should be considered for travellers to south-east Asia and the Far East who will be staying for a month or longer in endemic areas, especially if travel will include rural areas (C, IV).
- Under specific circumstances, vaccination should be considered for travellers spending <30 days in endemic areas (e.g. travellers to areas experiencing epidemic transmission) and persons whose activities place them at high risk for exposure (e.g. extensive outdoor activities in rural areas) (C, IV).
- The vaccine is also recommended for expatriates whose principal area of residence is an area where JEV is endemic or epidemic (C, IV).
- The recommended vaccine schedule is three doses on days 0, 7–14 and 28. The last dose should be administered at least 10 days before the commencement of travel to ensure an adequate immune response and access to medical care in the event of delayed adverse reactions. For those aged >60 years, an additional dose is recommended 1 month after completion of the initial course (C, IV).
- A booster is recommended after 3 years for those at continued risk (C, IV).
- The importance of precautions against mosquito bites should be emphasized.

9.5 Auditable outcomes

Proportion of at-risk HIV-infected patients who complete a three-dose vaccination course before travelling (target 70%).

10.0 Measles, mumps and rubella

10.1 Background

Measles virus and mumps virus are paramyxoviruses, whereas rubella is a togavirus. Measles, mumps and rubella are transmitted by the respiratory route. Measles is highly communicable. The incubation period is 10–12 days for measles, 14–18 days for mumps and 12–23 days for rubella.

Measles begins with a prodromal fever, conjunctivitis, coryza, cough, and Koplik spots on the buccal mucosa, followed by a maculopapular rash that lasts for 5–6 days. Complications include diarrhoea (8%), otitis media (7%), pneumonia (6%) and encephalitis (0.1%), leading to death in 2:1000 cases in developed countries.

Mumps begins with a prodromal febrile illness, typically followed by parotitis. Up to 30% of infections are asymptomatic. Neurological complications, usually mild aseptic meningitis, occur in up to 15% of symptomatic cases; permanent neurological sequelae are rare, including deafness (1:20 000 cases). Other complications are orchitis (20–50% of post-pubertal males) and pancreatitis (2–5%). The mortality rate is 1–3:10 000 cases.

Rubella is a mild illness characterized by low-grade fever, a maculopapular rash and generalized lymphadenopathy. In up to 70% of adult women it is complicated by arthralgia or arthritis. In the early months of pregnancy it is associated with a high rate of foetal loss or a constellation of birth defects, known as congenital rubella syndrome.

10.2 Epidemiology and risk groups

Measles, mumps and rubella remain common diseases in many countries of the world. Patients are at risk while travelling abroad [103], but may also be exposed to infection in the UK [104–106]. There is no evidence to suggest that mumps and rubella are more severe in the HIV setting. Measles, however, is potentially life-threatening. There may be no rash, and complications such as pneumonitis and encephalitis may present several months

after the initial infection [107,108]. Pregnant women are at risk of miscarriage after measles and are at risk of foetal damage after rubella infection.

Limited data on measles IgG seroprevalence among HIV-infected adults indicate higher rates in those born in the pre-vaccination era than in those born later [109]. A history of measles infection or immunization is not a reliable predictor of seropositive status [109], and seropositivity does not guarantee immunity [110]. High-titre high-avidity rubella IgG is initially maintained following HIV seroconversion but patients with AIDS show significantly lower titres [111].

10.3 MMR vaccine

The MMR vaccine contains live attenuated viruses [1]. In adults, two doses should be administered to confer protection again measles, with the second dose given at any time but at least 1 month after the first. One vaccine dose is required to confer protection against rubella. The MMR vaccine is given by deep subcutaneous or intramuscular injection, preferably in the deltoid.

10.3.1 Vaccine efficacy

In healthy persons, MMR is efficacious [1,112]. Susceptibility to measles is reduced to 10% following one dose of MMR, and 1% after two doses. Two vaccine doses induce sustained antibody titres to mumps and rubella in at least 95% of healthy recipients [1,112].

Limited published data show that a minority of measles IgG seronegative HIV-infected adults seroconvert following vaccination [113,114]. Seroconversion rates for rubella are also diminished in these patients. highly active antiretroviral therapy (HAART)-induced immunoreconstitution is likely to improve seroconversion rates. Children on HAART show improved serological responses to measles following MMR [115]. In healthy individuals protection is expected to be lifelong, but durability of responses may be reduced in HIV-infected persons.

10.3.2 Vaccine safety

Fever and rash occur in 5–15% of vaccine recipients, usually 7–12 days after vaccination and lasting 1–2 days; these are usually attributable to the measles component. Arthralgia and/or arthritis are reported in up to 25% of vaccinated women and are usually mild and transient. Transient lymphadenopathy sometimes occurs and is associated with rubella vaccination. Parotitis and deafness occur rarely and are attributable to the mumps component. Clinically apparent thrombocytopenia has been observed (<1 per 30 000 doses). Neurological complications, including aseptic meningitis, encephalitis and encephalopathy are very uncommon ($<1{:}1\,000\,000$ doses). Allergic reactions have been reported, but severe anaphylaxis is estimated to occur in $<1{:}1\,000\,000$ doses. With the exception of allergic reactions, other side effects are less frequent following the first dose and occur primarily among the small proportion of persons who did not respond to the first dose. MMR vaccinees do not act as a potential source of vaccine virus infection to their immunocompromised contacts [1].

In general, MMR vaccination is safe in HIV-infected adults; prior to 1993, it was advocated for both asymptomatic and symptomatic patients [116]. A change in policy was prompted by a case of fatal measles-vaccine-associated pneumonitis in a severely immunocompromised HIV-infected man, presenting almost 1 year after vaccination [117]. Vaccine-associated pneumonitis and encephalitis have also been described in other severely immunocompromised patients. Serious illnesses have not been reported in HIV-infected individuals in association with mumps or rubella vaccine administration.

10.3.3 Contraindications

- Pregnancy. Pregnancy should be avoided for 1 month after vaccination. The vaccine is not contraindicated in breast feeding women.
- Persons who are severely immunocompromised because of disease or treatment, including HIV-infected patients with CD4 counts <200 cells/μL.

10.4 Human normal immunoglobulin

HNIG affords short-lived pre-exposure protection against measles (approximately 3 weeks). HNIG is given by intramuscular injection (or subcutaneously in persons with bleeding disorders), preferably in the deltoid. HNIG causes minor local reactions and may cause an influenza-like illness and (rarely) anaphylaxis. It is contraindicated in those with a previous severe reaction.

10.5 Recommendations for measles, mumps and rubella pre-exposure prophylaxis in HIV-infected adults

- The combined MMR vaccine is recommended whenever one or more of the individual components are indicated.
- HIV-infected persons should be screened for measles IgG and the MMR vaccine offered to measles IgG-seronegative persons who are asymptomatic or mildly symptomatic with CD4 counts >200 cells/μL. Two doses should be given, with the second dose given at any time but at least 1 month after the first (C, IV).

- HIV-infected women of child-bearing age should also be screened for rubella IgG and the MMR vaccine offered to rubella IgG-seronegative women with CD4 counts >200 cells/μL. One MMR dose should be given (unless measles IgG-seronegative). Rubella IgG serology should be repeated after vaccination and a second MMR dose administered if the patient remains rubella IgG-seronegative (C, IV).
- Following immune restoration, MMR should be considered for measles IgG-seronegative individuals in whom vaccination was previously contraindicated (C, IV).
- Administration of HNIG (750 mg) should be considered as pre-exposure prophylaxis in measles IgG-negative persons who are severely immunocompromised and due to travel to countries where measles is endemic, bearing in mind that any protection afforded will be short-lived (C, IV).
- MMR should be administered at least 14 days before or 3 months after the administration of antibody-containing blood products (e.g. immune globulin), because passively acquired antibodies may interfere with the response to the vaccine.
- Measles-susceptible, healthy close contacts of HIV-infected individuals should receive two doses of MMR vaccine (C, IV).

10.6 Post-exposure prophylaxis

Because of the rapid induction of the measles antibody, contacts of measles may be protected by MMR vaccination administered within 3 days of exposure [1]. This is not the case for the mumps and rubella components. There are no data regarding the use of post-exposure MMR vaccination following measles exposure in individuals with HIV or other immunocompromised patients. HNIG can attenuate clinical measles in contacts but efficacy is not well defined in the immunocompromised [112,118–120]. There is no evidence to support the use of HNIG following exposure to mumps or rubella. Intravenous immunoglobulin (0.2 g/kg body weight) could be considered instead for persons in whom intramuscular injections are contraindicated.

10.7 Recommendations for measles post-exposure prophylaxis in HIV-infected adults

- Following a high-risk contact with measles, administration of HNIG (750 mg) is recommended for all HIV-infected persons regardless of vaccination or measles IgG serostatus (C, IV). The measles IgG serostatus should be determined, but neither prior vaccination nor detectable measles IgG ensure protection in the immunocompromised.
- HNIG should be given within 72 h and up to 6 days of exposure (C, IV).
- HNIG should be considered for susceptible pregnant women exposed to rubella or measles (C, IV).

10.8 Auditable outcomes

1. Screen HIV-infected persons for evidence of measles IgG (target 90%).
2. Screen HIV-infected women of child-bearing age for evidence of rubella IgG (target 75%).
3. Offer MMR vaccination to measles- and/or rubella-seronegative HIV patients who are neither pregnant nor severely immunocompromised (target 90%).

11.0 Meningococcus

11.1 Background

Neisseria meningitidis is a gram-negative bacterium. There are at least 13 serogroups including the clinically important A, B, C, Y and W135. Serogroups B and C are the most common in Europe, the Americas, Australia and New Zealand. Humans are the only known reservoir for *N. meningitides* and 5–11% of adults carry the bacterium in the nasopharynx in the absence of symptoms. Transmission occurs via the respiratory route during close contact and is often associated with overcrowded and poor conditions.

It is not fully understood why the disease develops in some individuals but not in others. *N. meningitidis* is a common and frequently devastating cause of meningitis and septicaemia in children and young adults. The incubation period is 2–7 days. The case fatality rate is approximately 10%; however, more deaths are caused by septicaemia than by meningitis. Less common manifestations include myocarditis, endocarditis, pericarditis, arthritis, conjunctivitis, urethritis, pharyngitis and cervicitis.

There is no evidence that infection by *N. meningitidis* is more common in HIV-infected individuals [121,122], although patients with lower CD4 cell counts may be more susceptible to less pathogenic strains of meningococci [123].

11.2 Epidemiology and risk groups

Since the introduction of routine infant immunization with the group C conjugate in the UK in the late 1990s, rates of group C meningococcal infection have fallen markedly in

this age group. Groups A and, increasingly, W135 are common epidemic strains in sub-Saharan Africa and the Middle East, respectively. The highest burden of meningococcal disease in the world occurs in the 'African meningitis belt', which extends across the dry, savannah parts of sub-Saharan Africa from Senegal in the west to Ethiopia in the east.

The following populations are at increased risk for meningococcal disease [1,124]:

- Household contacts of cases of meningococcal infection.
- Persons who travel to or reside in countries in which *N. meningitidis* is hyperendemic or epidemic. Travellers to these areas have a low risk of infection, which can be reduced further by avoiding overcrowded situations. The risk is higher for persons travelling to the 'meningitis belt' in sub-Saharan Africa during the dry season (December–June) and for those living or working in endemic and epidemic areas for prolonged periods.
- College students living in dormitories and military recruits.
- Microbiologists who are routinely exposed to isolates of *N. meningitidis*.
- Persons who have terminal complement component deficiencies.
- Persons who have anatomic or functional asplenia.

Other risk factors for meningococcal disease include antecedent viral infection, household crowding, chronic underlying illness, both active and passive smoking, bar or nightclub patronage and alcohol use during outbreaks [1].

11.3 Meningococcus vaccine

In the UK, several group C conjugate vaccines (MenC) and one quadrivalent vaccine (ACWY Vax) are available [1]. The vaccine is given by deep subcutaneous or intramuscular injection, preferably in the deltoid. MenC is recommended for all routine immunizations. It contains group C oligosaccharide conjugated to either diphtheria or tetanus protein, adsorbed on aluminium hydroxide. The quadrivalent vaccine contains A, C, W135 and Y polysaccharide; it is the vaccine of choice for travellers considered to be at risk and for persons in contact with serogroups A, C, W135 and Y. At present, there is no vaccine against serogroup B.

11.3.1 Vaccine efficacy

Large field trials of group A and C capsular polysaccharide vaccines in the 1960s and 1970s established their high efficacy (around 90%) in military recruits and children [125,126]. More recently, the immunogenicity (as a surrogate of clinical efficacy) of conjugate vaccines has been demonstrated in children [127,128]. MenC vaccines have an estimated clinical efficacy of $\geq$85% among school-aged children and adults. Since their introduction for routine vaccination of children and adolescents in the UK in the late 1990s, cases of group C disease have declined dramatically [129,130]. The protection afforded by the vaccines is strictly serogroup-specific. No boosting is recommended against meningococcal group C disease, although this is currently under review. Protection induced by the quadrivalent vaccine lasts for approximately 3–5 years. Boosters are recommended after 5 years for those at continuous risk

There have been very few data published on either the safety or efficacy of these vaccines in HIV-infected adults. Several reports of adequate serological responses to such vaccines are available, generally showing better responses in those with less advanced disease and no major adverse reactions [131–133]. The duration of protection may be reduced in HIV-infected persons, but there is insufficient evidence to modify the boosting recommendations.

11.3.2 Vaccine safety

Fever and injection site reactions are the most common adverse events reported. More serious (neurological) complications or anaphylaxis are very rare. There have been very few data published on safety in HIV-infected adults.

11.4 Recommendations for meningococcus pre-exposure prophylaxis in HIV-infected adults

- In agreement with current national guidelines, MenC vaccination is recommended in all HIV-infected young adults $<$25 years of age who have not previously received the vaccine or have uncertain immunization history (B, III). The vaccine is also recommended in HIV-infected adults of any age if at risk for meningococcus disease (B, III). These persons should generally receive one vaccine dose, but two doses are recommended in persons with asplenia or splenic dysfunction.
- The ACWY vaccine is recommended in HIV-infected adults at risk of infection through travel (B, III), including those who have previously received MenC vaccination. Proof of vaccination with the quadrivalent vaccine is required for visitors arriving in Saudi Arabia for the Hajj and Umrah pilgrimages. The vaccine is not otherwise recommended for travellers to areas outside Africa unless outbreaks occur. The vaccine should be considered for: (i) travellers who will be living or working with local people in an area of risk; (ii) long-

stay and rural travellers visiting areas of risk; (iii) backpackers; and (iv) travellers visiting an area of risk during an outbreak. These persons should receive one vaccine dose. If the risk recurs, a booster dose is recommended every 5 years (C, IV).
- HIV-infected adults who develop meningococcal disease should be offered one vaccine dose after recovery (C, IV).

11.5 Post-exposure prophylaxis

Contacts of confirmed cases of serogroup A, C, W135 or Y meningococcal disease should be offered vaccination, and also given chemoprophylaxis [1]. The recommended schedule for prophylaxis is rifampicin 600 mg every 12 h for 2 days in adults. Ciprofloxacin (500 mg once) may be used as an alternative in patients on ART. Rifampicin 600 mg twice daily for 2 days or intramuscular ceftriaxone 250 mg should be given to pregnant contacts [1].

11.6 Auditable outcomes

Documented administration of MenC vaccine in recommended groups (target 90%) and quadrivalent vaccine in travellers (target 90%).

12.0 Pertussis (whooping cough)

12.1 Background

Whooping cough is a highly contagious disease of the respiratory tract usually caused by the bacterium *Bordetella pertussis*. A similar illness can also be caused by *B. parapertussis* but this is not preventable with currently available vaccines. The disease is transmitted easily from an infected person via airborne droplets. The incubation period is 6–20 days. Pertussis ranges from a mild disease to one that is serious and can result in death. Infants and young children are most at risk of severe complications. Adults, older children and those partially protected by vaccination may still become infected but usually have milder disease.

12.2 Epidemiology and risk groups

Because of high vaccine coverage in the UK, pertussis is uncommon; there has been no epidemic in any age group since 1997 [134]. Pertussis has been diagnosed in HIV-infected adults and children, and should be considered as a cause of respiratory disease in persons with HIV [135–137]. However, current evidence does not suggest that pertussis is common among persons with HIV or that they are more likely to be a reservoir for *B. pertussis* in the community [138].

12.3 Pertussis vaccine

Pertussis vaccines licensed in the UK are inactivated acellular vaccines made from highly purified components of *B. pertussis* treated with formaldehyde or glutaraldehyde and adsorbed onto aluminium phosphate or hydroxide [1]. There are no pertussis-containing vaccines currently licensed in the UK for primary vaccination of persons over 10 years of age. A preparation combining acellular pertussis, low-dose diphtheria, tetanus and inactivated polio (dTaP/IPV) is licensed for use as a booster following a primary course of vaccination from 4 years of age. Vaccines formulated specifically for adolescents and adults who have completed a full primary course of pertussis in childhood are available in Australia, Canada, France and Germany. The pertussis vaccine is given intramuscularly (or subcutaneously in persons with bleeding disorders), preferably in the deltoid. The vaccine must not be administered by the intradermal or intravenous routes.

12.3.1 Vaccine efficacy

Pertussis vaccines are safe and immunogenic in immunocompetent adults [139]. Overall, the vaccines have a 75–90% efficacy against severe disease [1]. Immunization or infection with pertussis does not induce lifelong immunity, and the possible need for a pertussis booster for adolescents and adults in the future is currently under review [140]. Booster doses are not currently recommended in children over 10 years of age and adults. Pertussis vaccine combinations currently available for boosting in older children contain low doses of relevant antigens, and therefore may not offer high levels of protection in previously unvaccinated or partially vaccinated adults.

No data on the clinical efficacy of the pertussis vaccine in HIV-infected adults are available at this time. Antibody titres are lower in HIV-infected children compared to HIV-negative children and correlate with the CD4 cell count [141]. Patients in the earlier stages of infection are more likely to mount a protective antibody response.

12.3.2 Vaccine safety

Pain, swelling and redness at injection site are common side effects of the vaccine and may occur more frequently following subsequent doses. There is no increased risk of side effects or adverse reactions to vaccination in individuals with HIV infection.

12.4 Recommendations for pre-exposure pertussis prophylaxis in HIV-infected adults

- Pertussis vaccination in individuals aged 10 years and over is not recommended in the UK. In circumstances where an adult requires a full primary course of vaccination with diphtheria, tetanus and polio, the option of offering a combination that contains low doses of pertussis antigens could be considered (C, IV).
- For individuals at high risk of infection (for example those exposed in the household or in high-risk occupations), a single dose of a pertussis-containing vaccine could be considered (C, IV).

12.5 Post-exposure prophylaxis

Unimmunized or partially immunized individuals and vulnerable close contacts of a case of pertussis should be offered antibiotic prophylaxis within 21 days of onset of a clinically suspected or confirmed case [142]. Post-exposure prophylaxis is recommended in all HIV-infected persons regardless of CD4 cell count or immunization status. The recommended regimen for adults is erythromycin (250–500 mg 6 h) for 7 days. Clarithromycin may be considered as an alternative.

12.6 Auditable outcomes

Documented completion of primary vaccination (target 75%).

13.0 Pneumococcus

13.1 Background

Streptococcus pneumoniae, or pneumococcus, is a gram-positive bacterium. There are 90 serotypes and although all can cause infections, a few serotypes account for most cases of disease. Infection is acquired through direct person-to-person contact via respiratory droplets and by autoinoculation in persons carrying the bacteria in their upper respiratory tract. Pneumococci may be isolated from the nasopharynx of healthy persons in the absence of disease. The rate of asymptomatic carriage varies with age, environmental factors and the presence of other infections of the respiratory tract. The mechanisms that control the healthy carrier state *vs*. invasive disease are not understood. Pneumococci can cause: (i) pneumonia and other lower and upper respiratory tract infections (e.g. otitis media and sinusitis) and (ii) invasive pneumococcus disease (IPD), including bacteraemia and meningitis; the latter is frequently complicated by neurological sequelae. The incubation period is 1–3 days for pneumonia.

13.2 Epidemiology and risk groups

Pneumococcal disease occurs throughout the world, although geographically there is wide variation in the incidence of IPD. The greatest burden of disease is in developing countries. Infections are more common during the winter and in early spring. Rates of antibiotic resistance are increasing in many parts of the world and susceptibility to penicillin, cephalosporin and macrolides can no longer be assumed.

Infection is associated with significant mortality among young children in developing countries. Pneumococcal disease is also common in children in developed countries, but in these settings mortality is seen predominantly in the elderly ($\geq$ 65 years) and adults with underlying conditions, including:

- chronic cardiovascular disease;
- chronic pulmonary disease (e.g. chronic obstructive pulmonary disease or emphysema, but not asthma);
- chronic liver disease (cirrhosis);
- chronic renal disease;
- diabetes mellitus;
- absent or non-functioning spleen (e.g. sickle cell disease);
- hypogammaglobulinaemia;
- alcoholism;
- malnutrition;
- immunodeficiency caused by disease or treatment, including HIV infection [1,143].

Pneumococcus infection is a significant cause of pneumonia and IPD in HIV-infected persons [144]. Disease can occur early in the course of HIV infection and may recur. Paediatric serotypes are frequently involved and close contract with children is a recognized risk factor for infection. Risk factors for severe disease include low CD4 cell count, African race, HIV acquired via blood transfusion or injecting drug use, previous AIDS-defining opportunistic infections, previous pneumonia and alcoholism [145–147]. The annual attack rate of pneumococcal bacteraemia is as high as 1% among persons with AIDS [148]. Compared to HIV-negative adults, HIV-infected persons show an increased risk of mortality after controlling for age and severity of presentation, and the risk is related to CD4 cell count. Among hospitalized persons, the mortality rates are approximately 20% for pneumonia, 26% with bacteraemia without localizing signs and 65–75% for meningitis. The risk of antibiotic resistance is also higher in HIV-infected persons than in HIV-negative persons [149].

Since the advent of highly active antiretroviral therapy (HAART), the incidence of IPD has declined in the developed world [150–152]. Major risk factors for IPD in the HAART era are similar to those reported in HIV-negative individuals and include associated comorbidity, prior hospitalization, alcoholism and current smoking. Despite these improvements, the incidence of IPD remains substantially higher in HIV-positive persons than in similarly aged HIV-negative adults.

13.3 Pneumococcus vaccine

Two different vaccines have been developed: the pneumococcus polysaccharide vaccine (PPV) and the pneumococcus conjugated vaccine (CPV). The vaccine currently available in the UK for immunization of adults is known as PPV-23. This is composed of purified preparations of pneumococcal capsular polysaccharide from 23 different serotypes, which account for around 90% of cases of IPD. In addition, the vaccine induces cross-reactivity against serotypes that together account for an additional 8% of cases of IPD [1]. PPV-23 is given as a single dose by subcutaneous or intramuscular injection, preferably into the deltoid. The role and appropriate formulation of a CPV preparation for use in adults is currently under review.

13.3.1 Vaccine efficacy

More than 80% of healthy young adults who receive PPV-23 develop antibodies against the serotypes contained in the vaccine, usually within 2–3 weeks [1,143]. In older adults and persons with underlying conditions, responses are often reduced or absent. Elevated antibody levels persist for at least 5 years in healthy adults but decline more quickly in persons with underlying conditions. However, the relationship between antibody levels and protection from IPD is not certain. Routine boosting is not recommended in immunocompetent individuals previously vaccinated with the PPV-23 vaccine. Revaccination after 5–10 years of the first dose may be considered in high-risk groups in whom antibody levels are likely to decline [1].

Overall, PPV-23 is estimated to be 60–70% effective in preventing IPD, but may be less effective in those groups that also have the greatest risk of disease [143]. PPV-23 efficacy against non-bacteraemic pneumonia has not been demonstrated unequivocally. The original clinical trial performed in the 1970s in young healthy South African gold miners demonstrated a significant reduction in radiologically proven pneumonia among vaccine recipients. However, a subsequent meta-analysis showed that vaccination reduced bacteraemic pneumococcal pneumonia in low-risk adults, but did not show efficacy against non-bacteraemic pneumonia and in high-risk groups [153]. More recently, the use of CPV has shown efficacy in children in reducing the risk of IPD by 60–65% [154] and the risk of clinical lower respiratory tract disease by 15% [155]. Vaccinated children also showed a reduced risk of influenza-related hospitalization [156].

HIV-infected persons may have a diminished antibody response to pneumococcal vaccine and the reduction corresponds to the degree of immunodeficiency [83,84,157–163]. Responses are often lower in HIV-infected patients with CD4 counts < 500 cells/μL than in those with higher CD4 cell counts [158]. HAART is expected to improve efficacy of vaccination, but responses may remain sub-optimal, even after revaccination [164–166]. A prime-boost approach, using a CPV vaccine initially followed by PPV-23 boosting, appears to improve responses in both children [167] and adults [168]. This strategy may offer a way of improving responses but further data are required to allow the formulation of specific recommendations.

Studies on the clinical efficacy of pneumococcus vaccination in HIV-infected adults have reported inconsistent findings. Most have been conducted in persons not receiving antiretroviral therapy (ART) or receiving sub-optimal mono and dual therapy. In the only randomized controlled trial, the vaccine showed no efficacy in reducing the risk of pneumococcal disease among Ugandan HIV-infected persons not taking ART [169]. Surprisingly, there was a borderline increase in pneumonia of any cause in vaccine recipients (hazard ratio 1.89, 95% CI 1.1–3.2). Follow-up reports showed a persistent excess of 'all-cause' pneumonia in vaccine recipients – although, interestingly, a survival advantage was also observed [170]. No satisfactory explanation has been provided for these findings. However, several observational studies conducted in the USA did not identify increased risk associated with vaccination and most experts believe that the potential benefit of pneumococcal vaccination outweighs the risk in developed countries. One large prospective multi-centre observational study in the USA demonstrated a reduced incidence of pneumococcal disease in vaccine recipients with CD4 counts > 500 cells/μL, but not in those with lower CD4 cell counts [145]. Three further retrospective case–control studies also showed varying efficacy of the vaccine, depending on race and CD4 cell count [146,171–173].

Clinical efficacy data from patients on HAART are limited. One prospective study in Taiwan showed a significantly reduced incidence of pneumococcal disease in vaccine recipients, most of whom were taking HAART. However, persons in the control group were less likely to have received HAART and had an overall higher incidence of opportunistic infections [174]. In a Spanish prospective study, the odds ratios for developing pneumococcal pneumonia and IPD were 0.23 (95% CI 0.008–1.06) and

0.14 (95% CI 0.02–1.2), respectively, in vaccinated persons relative to unvaccinated persons [175].

The UK Department of Health recommendation for pneumococcal vaccination includes HIV infection at all stages [1]. American guidelines recommend vaccination for those with CD4 counts >200 cells/μL and indicate that vaccination should also be considered for patients with CD4 counts <200 cells/μL, although there is no clinical evidence of efficacy [176].

13.3.2 Vaccine safety

Injection site reactions occur in 30–50% of vaccine recipients but usually resolve within 48 h. Local reactions are reported more frequently following a second dose of PPV-23 than after the first dose, especially if less than 3 years has elapsed since the first injection. Systemic reactions with fever and myalgia occur uncommonly (<1%) and more serious adverse events are very rare.

13.3.3 Contraindication

Vaccination given within the previous 3 years [1]. However, when indicated, vaccine should be administered to patients who are uncertain about their vaccination history.

13.4 Recommendations for pneumococcus pre-exposure prophylaxis in HIV-infected adults

- There is conflicting evidence regarding the efficacy and safety of pneumococcal vaccination in HIV-infected adults. Overall, PPV-23 appears to be protective in patients on HAART, but the vaccine is likely to be less effective in drug-naïve patients with CD4 count <200 cells/μL, who are at the greatest risk of pneumococcal disease. On the balance of evidence, vaccination is recommended in HIV-infected adults with CD4 count >200 cells/μL and should be considered for those with CD4 count <200 cells/μL. In all patients, the indications for vaccination are strengthened in the presence of additional risk factors (C, IV).
- PPV-23 is given as a single dose. Booster doses are recommended every 5–10 years (C, IV).
- Vaccine failures should be monitored and reported.
- The role of CPV for adult vaccination, possibly as a prime-boosting approach with PIV-23, is currently under review and further information is awaited to inform these guidelines.

13.5 Auditable outcomes

The proportion of adults receiving the vaccine with CD4 counts >200 cells/μL.

14.0 Poliomyelitis

14.1 Background

Poliomyelitis is caused by the polioviruses serotypes 1, 2 and 3. Polioviruses are enteroviruses that replicate in gut mucosa, give rise to systemic infection and are characterized by neuro-invasiveness. They are spread by the faecal–oral and respiratory routes. The incubation period of polio is 3–21 days. Most infections are sub-clinical, but a minority give rise to neurological manifestations including aseptic meningitis, encephalomyelitis and the poliomyelitis syndrome, characterized by the acute onset of flaccid paralysis. The live attenuated oral polio virus vaccine (OPV) is shed asymptomatically in the stool of vaccinees for several days and shedding may be prolonged in immunocompromised persons [1,177,178]. The vaccine viruses can revert rapidly to virulence and may give rise to vaccine-associated paralytic polio (VAPP) in vaccinees or in their contacts [1,18].

14.2 Epidemiology and risk groups

As a result of continuing efforts to interrupt wild polio virus transmission, poliomyelitis continues to occur in only a few countries and is now exceedingly rare in the UK. The last indigenous case of wild-type infection was in 1984, and in the last decade the handful of cases have all been OPV-related VAPP. Susceptible adults may be at greater risk of paralytic polio than children. The estimated ratio of inapparent to paralytic infections is 75:1 in adults and 1000:1 in children [1]. Following OPV vaccination, immunocompromised persons are at greater risk of developing VAPP than healthy individuals [1,18]. Patients with hypogammaglobulinaemia have the greatest risk, but VAPP has also been reported in children with HIV infection [18,179,180]. No specific data are available on wild-type poliomyelitis in HIV-infected persons.

14.3 Polio vaccine

The OPV, comprising live attenuated strains of the three poliovirus sub-types, is no longer available routinely in the UK, having been replaced in 2004 with the enhanced inactivated poliovirus vaccine (IPV) in all routine vaccine schedules [1]. IPV contains the three serotypes of formaldehyde-inactivated poliovirus grown on monkey kidney cells. The IPV may be administered to adults as individual IPV vaccine or in combination with other vaccines, usually the combined diphtheria/tetanus/inactivated polio vaccine (Td/IPV). The recommended vaccination schedule is five vaccine doses. Any combination of

OPV and IPV can constitute a complete series. The vaccine is given intramuscularly (or subcutaneously in case of bleeding disorders), preferably in the deltoid.

14.3.1 Vaccine efficacy

The efficacy of current IPV preparations is greater than that of the original Salk IPV and is comparable to that of OPV [1]. Both OPV and IPV induce virus-neutralizing antibodies to polioviruses 1, 2 and 3, which confer significant protection against poliomyelitis. Following vaccination with IPV, antibodies to all three serotypes develop in >90% of healthy recipients after two doses and in >99% after three doses. With OPV, 50% of vaccine recipients are immune after one dose and >95% after three doses. Seroconversion rates after three doses of a combination of IPV and OPV are lower, particularly to type 3 vaccine virus [181]. OPV is likely to confer lifelong immunity. The duration of immunity conferred by IPV is not known, but in general childhood immunization with five doses is considered to give adequate long-term protection. One booster dose is recommended in adults at risk of exposure, for example through travel. The need for further supplementary doses has not been established and there is no evidence that following the administration of a booster dose in adult life, further doses are required for healthy individuals at repeated risk of exposure [182].

Both OPV and IPV can elicit neutralizing antibody responses in HIV-infected children [18]. Antibody responses to a primary course of IPV have been studied in children of HIV-infected mothers, comparing those with and without HIV infection. No significant differences were detected in the two groups, with 88% developing adequate titres of neutralizing antibody to all three serotypes after two doses of IPV, and 100% to at least two serotypes. However, responses were reduced in advanced disease [182,183]. The seroprevalence of poliovirus-neutralizing antibodies varies among HIV-infected adults. High prevalence rates, comparable to those in normal controls, have been reported in some cohorts. However, in a seroepidemiological study of Italian drug addicts, those with HIV infection were more likely to lack protection, with 34% seronegative for poliovirus type 1 and 11% lacking neutralizing antibodies to all three virus types [184].

In the pre-highly active antiretroviral therapy (HAART) era, boosting of poliovirus antibody titres was demonstrated in seropositive HIV-infected adults with a history of childhood vaccination following one dose of IPV [19,185,186]. However, antibody titres were generally lower in vaccinated HIV-positive individuals than in HIV-negative persons [185]. Responses were especially impaired in symptomatic individuals and in those with CD4 counts <300 cells/μL [19,185,186]. Presumably, humoral immune responses to IPV are restored in patients with advanced disease who are successfully treated with HAART [83]. However, the longevity of protection may be reduced in HIV-infected patients.

14.3.2 Vaccine safety

IPV can be administered safely to immunocompromised adults [1,187]. Injection site reactions are the most common adverse events reported, occurring with greater frequency after subsequent doses.

14.3.3 Contraindications

OPV is contraindicated in patients with HIV and their contacts.

14.4 Recommendations for polio pre-exposure prophylaxis in HIV-infected adults

- HIV-infected patients born and resident in the UK since 1962 have generally received a complete five-dose course of vaccination as part of routine childhood immunization. Provided the history of vaccination is reliable, no further doses are required unless there is a risk of exposure (C, IV).
- HIV-infected patients born in the UK before 1962 may not have been immunized. In the absence of a reliable history of vaccination, the opportunity to immunize them should not be missed. These patients should receive five IPV doses (C, IV).
- HIV-infected patients of any age and origin lacking a reliable history of vaccination should be offered five IPV doses (C, IV).
- Where indicated, the five doses should be administered as a primary course (three doses) given in three consecutive months with booster doses after 5 and 10 years.
- HIV-infected patients with a history of incomplete vaccination should receive the remaining doses of IPV to complete a five-dose vaccination course, regardless of the interval since the last dose and type of vaccine received previously (C, IV).
- HIV-infected patients who have completed a five-dose course of vaccination and are at risk of exposure (e.g. through travel) should be given one booster dose of IPV (C, IV). For patients with CD4 counts <300 cells/μL, antibody levels should be determined against the three poliovirus serotypes 4 weeks after the booster dose. Patients who remain susceptible should be advised not to travel (C, IV). If the risk of exposure recurs, asymptomatic patients with CD4 counts >300 cells/μL should be offered a single reinforcing dose every 10

years (C, IV). Further boosting doses should be considered in HIV-infected persons with CD4 counts <300 cells/μL at repeated risk of exposure.
- All travellers should be given advice about risk of infection through contaminated water and food and about the importance of hand hygiene (C, IV).

14.5 Post-exposure prophylaxis

HNIG can be used as post-exposure prophylaxis following inadvertent administration of OPV, exposure to a close contact given OPV or exposure to wild-type poliovirus. Because OPV is no longer available for routine use in the UK, direct or indirect exposure of HIV patients to OPV is likely to be an infrequent occurrence. Nevertheless, individuals with HIV infection may be exposed to OPV in the UK or while travelling through close or household contact with OPV recipients vaccinated abroad. There is no published evidence on the efficacy of HNIG in preventing or attenuating polio in immunocompromised individuals [120]. HNIG (750 mg) is given by deep intramuscular injection. It causes minor local reactions and may cause an influenza-like illness and, rarely, anaphylaxis. It is contraindicated in those with a previous severe reaction. Intravenous immunoglobulin (0.2 g/kg body weight) could be considered instead for persons in whom intramuscular injections are contraindicated.

14.6 Recommendations for polio post-exposure prophylaxis in HIV-infected adults

- HNIG (750 mg) is recommended for HIV-infected patients following exposure to wild-type poliovirus or OPV, regardless of vaccination history (C, IV).
- HNIG should be given as soon as possible after exposure. Protection lasts for 3 weeks.
- Where the information is available, HNIG is not indicated if the HIV patient is known to be antibody-positive to all three polio virus types.
- Prior OPV/IPV history should be recorded.
- A serum should be collected for baseline antibody testing, but prophylaxis should not be delayed pending the results. Stool samples should be collected 1 week apart for analysis. If poliovirus is detected, repeat administration of HNIG at 3-weekly intervals will be required until two consecutive stool samples test negative.

14.7 Auditable outcomes

Assess the vaccination history of HIV-infected patients and complete vaccination according to recommendations (target 80%).

15.0 Rabies

15.1 Background

Rabies is caused by viruses of the Lyssavirus genus, including the classic rabies virus genotype 1 and other related viruses [e.g. European Bat Lyssaviruses (EBLV)]. Rabies is transmitted by contact with a rabid animal, generally as the result of a bite or scratch. Transmission may also occur when infectious material, such as saliva or aerosolized secretions from an infected animal, comes into contact with mucous membranes or abraded skin, or on rare occasions through inhalation of virus-containing aerosol. Virus may be present in the saliva of patients with rabies, but person-to-person spread of the disease has not been documented with the exception of eight recipients of corneal grafts and seven recipients of solid organ transplants from donors unsuspected of having rabies [188,189].

The incubation period is 3–12 weeks (range 4 days–2 years or longer). Rabies classically presents as an acute encephalomyelitis and less commonly with an ascending flaccid paralysis. In both forms, coma and death follow almost invariably. Five cases of survival have been reported in people with rabies who had previously received pre- or post-exposure prophylaxis. A case of survival in the absence of any rabies immunization has been reported in a teenager with rabies who received an investigational regimen of antiviral therapy and induced coma [190].

15.2 Epidemiology and risk groups

Human rabies is common in most developing countries, where it occurs in both urban and rural areas [191]. Each year at least 55 000 people die from rabies in Asia and Africa. India alone reports 20 000 deaths per year [192]. In the majority of industrialized countries human rabies is under control, mainly because of oral vaccination of wildlife and mandatory vaccination of domestic animals [193]. No case of indigenous human rabies from terrestrial animals has been reported in the UK since 1902. The only indigenous human case of EBLV infection occurred in November 2002 in a bat handler who was bitten by a bat and did not receive pre- or post-exposure prophylaxis.

Animal rabies is widespread in every continent except Antarctica. In Asia, Africa and parts of Latin America both

stray and domestic dogs remain the principal vector and transmitter of rabies to humans. Canine rabies is endemic throughout most of these regions, and 90% of human cases with a defined source are caused by exposure to dogs, usually in the form of bites. The following are rabies reservoir species: wild mammals such as racoons, skunks, foxes and insectivorous bats in North America; vampire bats and mongooses in Central America; jackals, hyenas and mongooses in Africa; wolves, foxes and insectivorous bats in Europe; and fruit bats in Australia. In some parts of the world, other domestic and wild mammals such as cats and monkeys may transmit infection. In the UK, EBLVs have been detected in Daubenton's bats [194].

Risk of rabies by country is provided in the following sections [1]. This list is not exhaustive and may become out of date. For updated information on rabies by country, see the WHO websites (www.who.int/rabies and www.who-rabies-bulletin.org/) or the USA CDC websites (www.cdc.gov/ncidod/dvrd/rabies/epidemiology/epidemiology.htm and www2.ncid.cdc.gov/travel/yb/utils/ybGet.asp?section=dis&obj=rabies.htm&cssNav=browseoyb).

15.2.1 No risk from terrestrial mammals (i.e. excluding bats)

- Europe: Austria, Belgium, the Canary Islands, Cyprus, Denmark, Faroe Islands, Finland, France, Gibraltar, Greece, Iceland, Ireland, Italy (except the northern and eastern borders), Luxembourg, Malta, Netherlands, mainland Norway, Portugal, mainland Spain (excluding the north African coast), Sweden, Switzerland, UK.
- Americas: Anguilla, Antigua and Barbuda, Bahamas, Barbados, Bermuda, British Virgin Islands, Cayman Islands, Dominica, Equatorial Guinea, French Antilles, Guadeloupe, Jamaica, Martinique, Montserrat, Netherlands Antilles, St Christopher and Nevis, St Lucia, St Martin, St Pierre and Miquelon, St Vincent and the Grenadines, Turks and Caicos, Uruguay, Virgin Islands.
- Asia: Bahrain, Brunei, Darussalam, Hong Kong, Japan, Kuwait, Maldives, Qatar, Singapore, Taiwan.
- Oceania: American Samoa, Australia, Belau, Cook Islands, Federated States of Micronesia, Fiji, French Polynesia, Guam, Kiribati, Marshall Islands, New Caledonia, New Zealand, Niue, Northern Mariana Islands, Papua New Guinea, Samoa, Sao Tome and Principe, Solomon Islands, Tonga, Vanuatu and Western Samoa.

15.2.2 Low risk

- Europe: Bulgaria, Czech Republic, Germany.
- Americas: Canada, USA (see the CDC website for information on the risk of rabies in different parts of the USA).

15.2.3 High risk

Colombia, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, India, parts of Mexico, Nepal, Pakistan, Peru, Philippines, Sri Lanka, Thailand, Turkey, Vietnam. Countries in Asia, Africa and South America not otherwise mentioned as 'no risk' or 'low risk' should be considered as 'high risk'.

Persons at risk of infection include laboratory workers handling the virus, veterinarians, animal handlers including bat handlers, wildlife officers, persons who regularly explore or hike in caves, healthcare workers caring for patients with rabies and travellers to highly rabies-enzootic areas. In the UK the greatest risk is among travellers and in persons who come in close contact with imported animals or indigenous bats.

HIV-infected persons are at risk of rabies if they belong to a group at recognized risk of exposure. There are no published data to indicate that the clinical manifestations of rabies encephalitis are modified by HIV infection. Although extremely unlikely, HIV-infected persons could be at risk of adverse events if exposed to the veterinary oral live viral vaccines, which, placed in bait, are used for disease control in wildlife in Europe and North America.

15.3 Rabies vaccine

The human rabies vaccines are inactivated. There are currently two licensed rabies vaccines for use in the UK: the rabies human diploid cell vaccine (HDCV) and the purified chick embryo cell rabies vaccine (PCEC), which are interchangeable [1]. Vaccines of nerve tissue origin are still in use in some developing countries. These are reactogenic and some are of low immunogenicity.

For both pre- and post-exposure prophylaxis, vaccine is administered intramuscularly (or subcutaneously in persons with bleeding disorders), preferably into the deltoid region. The antibody response may be reduced if the gluteal region is used or if the vaccine is injected into fat. Intradermal administration of smaller vaccine doses is used in some developing countries to reduce vaccination costs, but for pre-exposure treatment it may result in reduced immune responses [195,196].

15.3.1 Vaccine efficacy

Three intramuscular doses of HDCV for pre-exposure vaccination produce a satisfactory antibody response (neutralizing antibody level >0.5 IU/mL) in over 99% of recipients. Post-exposure treatment initiated at an early stage is nearly 100% effective in preventing rabies, but delayed or incomplete treatment results in human deaths, often associated with severe lesions on or near the head or hand. High-dose steroids and any other immunosuppression

may reduce vaccine efficacy. In over 96% of healthy vaccine recipients, rabies-neutralizing antibodies persist for at least 10 years after primary pre-exposure vaccination with a cell vaccine followed by a single booster dose after 1 year.

Data on the efficacy of rabies vaccine for pre- and post-exposure prophylaxis in HIV-positive persons are very limited. Available evidence indicates that the immune response is affected by the CD4 cell count and disease stage, with low or absent antibody responses reported in some persons with CD4 counts <200–250 cells/μL [197–200]. In published studies, most vaccine failures occurred in persons who were either not receiving ART or were receiving sub-optimal regimens. It is likely that highly active antiretroviral therapy (HAART)-induced immunoreconstitution improves responses to rabies vaccination. Repeat vaccine course, double dose vaccine and more frequent boosting doses have been proposed as management options for HIV-positive patients who fail to mount an acceptable antibody response, but there are insufficient data to give firm recommendations. The duration of immunity in HIV-infected persons is unknown.

15.3.2 Vaccine safety

Although associated with mild and transient reactions, all the cell-derived rabies vaccines are considered safe [196,201]. With HDCV, injection site reactions occur in 30–74% of vaccinees within 24–48 h of administration. Mild systemic reactions with headache, nausea, abdominal pain, muscle aches or dizziness are reported in 5–40% of vaccinees. Systemic allergic reactions are uncommon in primary vaccination, but occur in up to 6% of persons receiving a booster dose. Guillain–Barré syndrome has been observed extremely rarely. In the few studies reported, the rabies vaccines were tolerated well in HIV-infected persons [197–200].

Inactivated vaccines produced in sheep or goat brains (Semple) or suckling mouse brain (Fuenzalida) are in use in a few developing countries and may be offered to travellers exposed to animal bites. They can be associated with serious and even fatal autoimmune neurological adverse events. Their use is not generally recommended in anyone, especially HIV-positive individuals, because they may be weak antigens, but they are better than no vaccine at all for those exposed to rabies.

15.3.3 Contraindications

Pre-exposure prophylaxis:

- If antimalarial chemoprophylaxis with chloroquine is used, vaccine must be given intramuscularly not intradermally.

Post-exposure prophylaxis:

- There are no absolute contraindications. Hypersensitivity reactions can occur and caution is required in persons known to be sensitive to neomycin, amphotericin B or chlortetracycline. If an allergic reaction occurs, the risk of developing rabies should be considered before deciding to discontinue post-exposure immunization. Management options include pre-treatment with antihistamines and the use of a vaccine of a different cell substrate origin, under medical supervision.
- Concomitant steroids are contraindicated because of the increased mortality noted in animal studies and because they reduce the response to the vaccine

15.3.4 Pre- and post-vaccination testing

A rabies-neutralizing antibody level >0.5 IU/mL is considered the minimal adequate response indicating unequivocal seroconversion [196]. Pre-vaccination serology is advised to vaccine candidates who have had a severe reaction to a previous vaccine dose to confirm the need for a reinforcing dose. Post-vaccination serology is used to guide boosting requirements in persons with regular and continuous exposure to rabies. Post-vaccination serology may also be indicated in immunocompromised persons. Rabies serology is available at the Veterinary Laboratories Agency, Weybridge Head Office (Woodham Lane, New Haw, Addlestone, Surrey KT15 3NB; tel: + 44 1932 341 111; www.vla.gov.uk).

15.4 Rabies immunoglobulin

The human rabies immunoglobulin (HRIG) is prepared from plasma of hyperimmunized human donors. In developing countries, equine rabies immunoglobulin (ERIG) is sometimes used, but it has a higher incidence of adverse effects and the quality of the product may vary. HRIG is administered for all primary post-exposure prophylaxis. The entire dose (20 IU/kg) is infiltrated, if anatomically possible, in and around the site of exposure, with any remaining solution administered intramuscularly at a site different from that used for the vaccine. The recommended dose of 20 IU/kg should not be exceeded because higher doses are associated with reduced antibody response to vaccine.

Reactions with HRIG include local pain and low-grade fever. No serious adverse reactions have been reported. ERIG has a higher incidence of adverse effects, which includes serum sickness but usually involves minor reactions. Rabies immunoglobulin is never contraindicated in documented hypersensitivity, but adrenaline should always be at hand.

15.5 Recommendations for rabies pre-exposure prophylaxis in HIV-infected adults

Travellers:

- Vaccination is recommended in all HIV-infected persons who are due to travel to dog-rabies endemic areas (B, III). Pre-exposure prophylaxis is most important for those with CD4 counts <200 cells/μL because of uncertainties about the efficacy of post-exposure prophylaxis and most appropriate immunization schedules (C, IV).
- Three intramuscular vaccine doses should be given on days 0, 7 and 28. Advancing the third dose to day 21 is not recommended because it may curtail the immune response (B, III).
- Intradermal vaccination for pre-exposure prophylaxis may result in lower immune responses and is not recommended for HIV-infected persons (C, IV).
- Patients with CD4 counts <200 cells/μL, nadir CD4 counts <200 cells/μL and current or previously symptomatic disease may show reduced responses to rabies vaccination. Where there is a doubt about efficacy, serological testing to assess the antibody response to vaccination should be considered (B, III). Testing should be performed 2–4 weeks after the last vaccine dose. If an acceptable (>0.5 IU/mL) antibody response is not achieved, a further booster dose of rabies vaccine should be administered and the antibody response rechecked (C, IV). Exposure must be avoided in those who fail to mount an acceptable antibody response after the booster dose (C, IV).
- If the risk of travel-related exposure recurs, a first booster is indicated 1 year after the primary course. Subsequent boosters are given after 3–5 years. In HIV-infected persons with severe immunodeficiency, serological testing should be considered to assess antibody responses after boosting (B, III).
- Pre-exposure prophylaxis does not eliminate the need for wound management and for post-exposure immunization. All travellers to enzootic areas should be informed of the practical steps to be taken if an animal bite is sustained and instructed to have immediate vaccine boosters. Travellers should be instructed on wound treatment procedures because they are very important as a first aid.

Regular or continuous exposure in the occupational setting:

- Until more data are available on the effect of HAART on responses to rabies vaccination, regular or continuous occupational exposure should be avoided in HIV-infected persons with CD4 counts <400 cells/μL, nadir CD4 counts <200 cells/μL and currently or previously symptomatic disease (B, III). Other HIV-infected persons should be offered pre-exposure vaccination according to general guidelines and serological testing should be performed 2–4 weeks after the last vaccine dose (C, IV).
- If an acceptable (>0.5 IU/mL) antibody response is not achieved, a booster dose should be administered and the antibody response rechecked (C, IV). Exposure must be avoided in those who fail to mount an acceptable antibody response after the booster dose (C, IV).
- For those who have responded to the primary vaccine course (antibody level >0.5 IU/mL), antibody tests should be performed every 6–24 months, depending on level of risk, to determine the need for booster doses (BIII).

15.6 Recommendations for rabies post-exposure prophylaxis in HIV-infected adults

- Given the limited evidence, each case should be assessed individually using serological testing and expert advice as a guide (see Table 10). Caution is required for patients with CD4 counts <200 cells/μL, nadir CD4 counts <200 cells/μL and current or previous symptomatic disease, because responses to vaccination may be reduced. It is likely that HAART-induced immunoreconstitution improves responses to vaccination.
- Post-exposure prophylaxis must be started as soon as possible after a suspected exposure. Because the incubation period for rabies can be prolonged, treatment should still be considered whatever the interval from exposure.
- As soon as possible after the incident, the wound should be cleansed thoroughly for a minimum of 5 min by scrubbing with copious soap into the depth of the wound, and water under a running tap, followed by either 70% ethanol or povidone iodine.
- The local doctor should be consulted because the risk of rabies differs geographically based on local endemicity and immunization practices. For updated information on rabies by country, consult WHO (www.who.int/rabies/) or CDC (www.cdc.gov/ncidod/dvrd/rabies/epidemiology/epidemiology.htm).
- Information must be collected on: the site and severity of the wound; the circumstances of the exposure; the species, behaviour, appearance, vaccination status and origin of the animal; the location of the incident; and the incidence of rabies in that species and in that country.
- Post-exposure prophylaxis of healthcare workers is indicated only for high-risk exposures, including contamination of mucous membranes or open wounds by saliva, tears, cerebrospinal fluid or neurological tissue.

Table 10 Schedule for rabies post-exposure prophylaxis in HIV-infected adults

Treatment	Previously vaccinated appropriately; currently asymptomatic with CD4 counts >400 cells/μL*	Others
Wound care: cleaning and leaving open	Yes	Yes
HRIG on day 0	No	Yes†
Intramuscular Rabies Vaccine‡,§	Two doses on days 0, 3	Five doses on days 0, 3, 7, 14, 30. Alternatively, ¶2–1–1 regimen on days 0, 7, 21
Serological testing ‖	After day 14	After day 14

HRIG, human rabies immunoglobulin.
*Each case should be assessed individually. This category excludes persons who have received fewer than three vaccine doses previously, have uncertain vaccination history, had previous vaccination but showed an antibody response <0.5 IU/mL, had a CD4 count <400 cells/μL at the time of previous vaccination and no post-vaccine serological testing, or are currently symptomatic. If there is any uncertainty, a full post-exposure regimen should be given (B, III).
†In countries classified as low risk, HRIG may not be required but each case should be assessed individually. Current guidelines indicate that if HRIG is not available until >7 days after vaccination has started, then it is unnecessary because an active antibody response has already begun. However, HRIG should be considered for HIV-positive patients even if vaccination was started >7 days previously (C, IV). Repeated doses of HRIG should not be administered once vaccination has been initiated to prevent interference with the vaccine immunogenicity (C, IV).
‡All intramuscular injections must be given into the deltoid region. Vaccine should never be injected into the gluteal region. Rabies vaccine and HRIG should not be given with the same syringe or in the same site.
§Some developing countries use economical multi-site intradermal regimens for post-exposure vaccination. In these settings, HIV-infected persons should preferably receive the standard intramuscular regimen (C, IV).
¶The abbreviated course is followed in some countries. It consists of two doses on day 0 (one in each deltoid), followed by one dose on day 7 and one dose on day 21.
‖ Serological testing between days 14 and 28 is suggested in all HIV-positive persons and is strongly recommended in those who have a CD4 count <200 cells/μL (BIII). If an acceptable (>0.5 IU/mL) antibody response is not achieved, a further booster dose of rabies vaccine should be administered (C, IV).

- Vaccines of nerve tissue origin are not recommended in HIV-infected persons but they are better than no vaccine at all (C, IV). Efforts should be made to obtain cell culture vaccines as soon as possible for post-exposure prophylaxis.

15.7 Auditable outcomes

Discuss rabies prophylaxis before travel to high-risk areas (target 95%).

16.0 Smallpox

16.1 Background

Smallpox is caused by Variola virus, a member of the orthopoxviridae family. The infection is spread through direct contact with droplets and to a lesser extent through aerosol. The most common mode of transmission is through close, face-to-face contact with an infectious individual. There are two clinical variants: Variola major (mortality up to 30%) and Variola minor (mortality up to 5%).

Following a worldwide vaccination campaign, smallpox was declared eradicated from the world in 1980 and routine vaccination stopped. Vaccine programmes have recently been restarted in several countries in response to a hypothetical threat from bioterrorism [202,203]. The vaccine has been offered to some healthcare workers and ambulance staff in the UK to provide a frontline response to a case of suspected smallpox. Laboratory workers are also vaccinated against this disease.

16.2 Smallpox vaccine

The smallpox vaccine is a live vaccine prepared with vaccinia virus. The vaccine is given as a single dose via a bifurcated needle applied to the dorsal aspect of the skin of the upper arm. Successful vaccination is indicated by characteristic skin reaction, which develops after 3–4 days.

16.2.1 Vaccine efficacy

In healthy persons, the vaccine is at least 95% effective in inducing protective immunity. A booster dose is recommended after 3 years. Revaccinated people may be protected for at least 10 years. Vaccination within 3 days of exposure prevents disease or reduces its severity. Partial protection is observed if post-exposure prophylaxis is started after 4–7 days.

16.2.2 Vaccine safety

Successful vaccination is normally associated with tenderness, redness, swelling and a lesion at the vaccination site. Vaccination may also be associated with fever and enlarged, tender lymph nodes in the axilla of the vaccinated arm [203]. A vaccinated person can transmit the vaccine virus directly through contact with the injection site and indirectly through objects that come in contact with the area around the vaccination site, including clothes, bedding, bandages and furniture. Infectivity lasts until the vaccination wound has healed and the scab has fallen off, usually within 14–21 days.

The smallpox vaccine is not as safe as modern vaccines. In the past, vaccine-related fatalities were reported in approximately one per million vaccinations. Complications may include:

- Generalized vaccinia: characterized by a generalized rash; may occur in healthy individuals and has a good prognosis.
- Foetal vaccinia: may occur in vaccinated pregnant women and result in loss of pregnancy or stillbirth.
- Encephalitis: the most serious complication; occurs more commonly in children, with a 35% risk of mortality and common sequelae.
- Pericarditis.
- Eczema vaccinatum: characterized by spread of vaccinia virus in eczematous skin with localized or generalized lesions; it may be life-threatening in infants.
- Vaccinia gladiatorum: accidental inoculation of vaccinia into other sites in the vaccinated individual or close contacts; this is not a major concern unless the eye is involved.
- Vaccinia necrosum (progressive vaccinia): occurs in immunosuppressed individuals and is characterized by a slow and uncontrolled growth of vaccinia virus at the site of inoculation, frequently complicated by viraemia and generalized infection involving skin and multiple organs, with a 40–80% risk of mortality.

Immunocompromised patients are at increased risk for adverse events. In HIV-infected persons, the overall risk of progressive vaccinia is probably <1 per 300 and related to CD4 cell count. There is one case report of progressive vaccinia in a military recruit who received smallpox vaccination in 1984 [204]. However, several hundred HIV-infected military recruits received the vaccine without known complications. In a study of 10 asymptomatic military recruits with a CD4 count of 286–751 cells/μL, the vaccine was tolerated well and induced a normal, robust response without complications [205]. Immunoreconstitution with highly active antiretroviral therapy (HAART) is probably the best method to prevent vaccine-related complications.

In the past, high doses of vaccinia immunoglobulin (VIG) derived from immunized individuals appeared to be effective in halting a proportion of cases of progressive vaccinia. VIG was most effective in patients with less severe immunological defects [206–208]. The experience with VIG for the treatment of progressive vaccinia in persons with AIDS is limited to one reported case [204].

16.2.3 Contraindications

- Pregnancy and breast feeding.
- Current or past eczema and atopic dermatitis, or a current significant skin condition (e.g. burns, impetigo, chickenpox, contact dermatitis, shingles, herpes, severe acne, keratosis follicularis, psoriasis).
- Persons with immunodeficiency caused by disease or treatment, including HIV-infected persons [203].

16.3 Recommendations for smallpox prophylaxis in HIV-infected adults

- All smallpox vaccine candidates should be made aware that the vaccine may pose a risk to people with HIV. HIV testing should be offered to those who wish to be tested prior to vaccination, although it should not be mandatory (C, IV).
- Where vaccination is being proposed for an HIV-infected person, a risk–benefit assessment should be made of the risk of contracting smallpox *vs*. the risk of vaccine-related side effects. In the absence of recognized risk of infection, the risks of pre-emptive vaccination outweigh the benefits and vaccination is therefore not recommended (C, IV).
- Post-exposure vaccination following a high-risk contact should be offered to all HIV-infected patients (C, IV).
- HIV-infected vaccine recipients who experience complications from the vaccine should receive VIG and intravenous cidofovir (C, IV).
- HIV-negative vaccine recipients who are close contacts of HIV-infected persons should be given advice as to how to reduce the risk of transmission of the vaccine virus through direct or indirect contact with the vaccine reaction site (C, IV).

17.0 Tetanus

17.1 Background

Tetanus is caused by the action of a neurotoxin (tetanospasmin) released by the gram-positive, anaerobic bacterium *Clostridium tetani*. The bacterium and its spores are found primarily in the soil and intestinal tracts of animals and humans. Transmission occurs when spores are introduced into the body, typically through puncture wounds, burns and scratches, but also through trivial, unnoticed wounds, injecting drug use and occasionally abdominal surgery. Tetanus spores are widely distributed in soil or manure and may be introduced to a wound easily following an injury. The spores can also be found on skin surfaces and in contaminated heroin and drug paraphernalia. In the presence of anaerobic conditions, the spores germinate and the toxins are produced and released systemically. Tetanus is not contagious from person to person.

The incubation period of tetanus is usually 4–21 days (range 1 day to several months). In general the length of

the incubation period is inversely correlated with the distance from the central nervous system; the shorter the incubation period, the higher the risk of death. In its most common manifestation, the disease is characterized by generalized rigidity and spasms of skeletal muscles and can lead to respiratory and cardiac failure. The case fatality ratio is 29% overall, but ranges from 10 to 90%. Recovery from tetanus may not result in immunity, and vaccination following tetanus is indicated.

17.2 Epidemiology and risk groups

Tetanus occurs worldwide but is most common in densely populated regions in hot, damp climates with soil rich in organic matter. On average 10 cases are reported in the UK each year, mostly in elderly unvaccinated individuals. A recent increase in cases in injecting drug users has been observed. Tetanus has occurred only rarely among persons who had previously received a primary vaccine course. The proportions of persons lacking protective levels of circulating antitoxins against tetanus increase with age; at least 40% of those aged ≥ 60 years may lack protection. It is not known whether the natural history of tetanus is modified by HIV infection.

17.3 Tetanus vaccine

The tetanus vaccine is made from cell-free purified toxin extracted from *C. tetani*, treated with formaldehyde, converted into tetanus toxoid and adsorbed onto aluminium phosphate or hydroxide. The vaccine is generally given to adults as a combined tetanus, low-dose diphtheria and inactivated polio vaccine (Td/IPV), which has replaced single antigen tetanus (T) and tetanus/low-dose diphtheria (Td) vaccines [1]. The vaccine is administered intramuscularly (or subcutaneously in persons with bleeding disorders), preferably in the deltoid. The vaccine must not be administered via the intradermal or intravenous routes.

17.3.1 Vaccine efficacy

In healthy persons the tetanus vaccine is highly immunogenic and effective [209]. Although antitoxin levels decrease with age, the majority of vaccinated adults maintain protective antitoxin levels for many years [210]. A total of five doses of tetanus vaccine at the appropriate intervals are considered to give lifelong immunity. Boosters are recommended every 10 years for those at risk.

The vaccine has been shown to be immunogenic in a variety of immunocompromised hosts [18,83,211] including HIV-infected adults [20,21] – although less so than in HIV-negative persons [212,213]. In HIV-infected children, serological response rates are 60–100% after primary vaccination and 75–90% after booster vaccination [214]. Although these children show lower serum antitoxin levels compared to controls, a substantial proportion demonstrate antibody levels that are considered protective. Adults who received full primary vaccination before acquiring HIV infection may have sufficient humoral immunity for several years and are likely to develop protective levels of antitoxin following a booster dose [215]. Patients in the earlier stages of infection are more likely to mount a protective antibody response than those with HIV-related symptoms [83]. As a general rule, responses are inversely correlated to the CD4 cell count. Antibodies in HIV-infected persons may decline to non-protective levels as immune function deteriorates, but there is insufficient evidence to modify recommendations about boosting.

17.3.2 Vaccine safety

Injection site reactions are common but usually self-limited and may occur more frequently following subsequent doses. Fever and other systemic reactions are uncommon. Severe systemic reactions such as generalized urticaria, anaphylaxis or neurological complications have been reported rarely. There is no increased risk of side effects or adverse reactions in individuals with HIV infection.

17.4 Recommendations for tetanus pre-exposure prophylaxis in HIV-infected adults

- Tetanus vaccination is recommended in all HIV-positive persons regardless of CD4 cell count and should be given in accordance with standard recommendations (C, IV). Adults who have not been immunized previously or have an uncertain vaccination history require five vaccine doses in order to confer adequate protection. Three doses should be given at least 1 month apart and further boosting doses should be planned at 5 and 10 years. There is no need to restart a series if more than the recommended time between doses has elapsed.
- Adults who have received a full primary course (three doses) as infants and a booster at pre-school age (total of four doses) require a single booster dose (C, IV).
- Persons who have received five vaccine doses require a booster dose at 10-yearly intervals if they are due to travel to remote areas where they may not be able to receive tetanus immunoglobulin (TIG) in the event of a tetanus-prone injury (C, IV).

17.5 Post-exposure prophylaxis

In unvaccinated persons, the tetanus vaccine alone is not considered adequate for post-exposure prophylaxis after a

Table 11 Recommendations for tetanus post-exposure prophylaxis in HIV-infected adults

Vaccination history	Clean minor wound, negligible risk*		Other wounds	
	Vaccine†	TIG	Vaccine	TIG‡
Uncertain or <3 doses	Yes (three doses)	No	Yes (three doses)	Yes
Three or more doses	Yes (one dose) if last dose given >10 years before	No	Yes (one dose) if last dose given >10 years before or CD4 count <200 cells/μL	Yes§

TIG, tetanus immunoglobulin.
*Tetanus-prone wounds:
- Wounds or burns that require surgical intervention and when that treatment is delayed for more than 6 h;
- Wounds or burns that show any of the following characteristics: a significant degree of devitalized tissue, puncture-type injury particularly in contact with soil or manure;
- Wounds containing foreign bodies;
- Compound fractures;
- Wounds or burns in patients who have systemic sepsis.

†Tetanus vaccine is recommended in all HIV-infected persons following a possible exposure (B, III).
‡TIG should be given by intramuscular injection in the deltoid within 24 h of possible exposure. When tetanus vaccine and TIG are given concurrently, separate syringes and separate sites should be used.
§TIG is not usually indicated for persons who have received at least three vaccine doses including a dose within the previous 10 years. However, individuals with a high-risk wound who are severely immunosuppressed should receive TIG even if fully vaccinated in the past and where the last vaccine dose occurred within the last 10 years (C, IV).

high-risk exposure. Patients with unknown or uncertain previous vaccination history and those who have not completed the primary vaccine series should also be considered susceptible. TIG is used for post-exposure prophylaxis in these patients together with the tetanus vaccine (see Table 11). TIG is given by intramuscular injection at the dose of 250 IU, or 500 IU if more than 24 h have elapsed since injury, if there is a risk of heavy contamination and following burns [1]. TIG confers protection for approximately 4 weeks [215]. TIG has not been studied in large-scale trials. Evidence of its efficacy has been drawn from retrospective studies in healthy individuals. Efficacy in HIV-infected persons has not been established.

Wound cleaning, debridement (when indicated) and proper immunization are the essential components of wound management in HIV-infected persons. The need for tetanus vaccine and TIG depends on both the condition of the wound and the vaccination history.

17.6 Auditable outcomes

Documentation of the completion of primary vaccination (target 75%).

18.0 Tick-borne encephalitis

18.1 Background

Tick-borne encephalitis (TBE) is caused by the tick-borne encephalitis virus (TBEV), a member of the flaviridae. Two closely related sub-types – Western (TBEV) and Eastern [Russian Spring–Summer Encephalitis virus (RSSEV)] – exist, causing similar diseases. The infection is transmitted to humans by the bite of an infected tick or, less commonly, by ingestion of unpasteurized milk from infected animals, mainly goats. Person-to-person transmission has not been reported. The incubation period is 7–14 days (range 2–28 days). The typical course of TBE is biphasic. The first stage is characterized by non-specific influenza-like symptoms that last 1–8 days. Following an afebrile period of 1–20 days, central nervous system involvement can manifest as meningitis, encephalitis or meningoencephalitis. Only about one third of those with symptomatic infection proceed into the second phase of the disease, which may lead to neurological sequelae in 10–20% of patients. The case fatality rate is 1–2%. Disease caused by the Eastern sub-type runs a similar course but carries a 20% risk of mortality. There is no specific drug therapy.

18.2 Epidemiology and risk groups

Infections occur in many parts of Europe, the former Soviet Union and Asia, corresponding to the distribution of the tick reservoir. The distribution covers almost the entire southern part of the Eurasian forest belt, from Alsace-Lorraine in the West to Vladivostok and northern and eastern regions of China in the East, through to northern Japan. The disease occurs in most or parts of Austria, Germany, southern and central Sweden, Hungary, France (Alsace), Switzerland, Norway, Denmark, Poland, Croatia, Albania, the Baltic states (Estonia, Latvia and Lithuania), the Czech Republic, Slovakia, Hungary, Russia and western Siberia and countries of the former Soviet Union. Many endemic countries have adopted national vaccination programmes. There are two seasonal peaks in central Europe, one in June/July and the second in September/October, corresponding to two waves of feeding by tick larvae and nymphs.

Generally, the risk to the average traveller to affected countries is small. Infections are related to either leisure activities such as hiking, walking and hunting, or working in agriculture and forestry in warm, rural or forested parts of endemic regions. Men tend to be affected more frequently than women. People at risk of infection include foresters, woodcutters, farmers, military personnel, laboratory workers

Table 12 Schedule of TBE vaccination

	FSME-Immun	Encepur
Standard schedule		
Primary course	Two doses 3–12 weeks apart	Two doses 4–12 weeks apart
Third dose	9–12 months later	9–12 months later
Rapid schedule		
Primary course	Two doses 14 days apart	Three doses on days 0, 7 and 21
Third dose	9–12 months later	N/A
Fourth dose	N/A	12–18 months later

and tourists who camp, hunt and undertake field work in rural, forested areas.

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

18.3 TBE vaccine

Two inactivated whole-virus vaccines are available in Europe. The FSME-Immun is prepared with the Neudorfl strain. The Encepur is prepared with the K23 strain.

The vaccines can be given in a standard or rapid schedule (see Table 12). The vaccine is given intramuscularly (or subcutaneously in persons with bleeding disorders), preferably in the deltoid.

18.3.1 Vaccine efficacy

The vaccine protects against infection with both TBEV and RSSEV. In healthy persons, the rate of seroconversion after three doses is 85–100%. However, only 52% of vaccine recipients maintain protective antibody levels 42 months after the third immunization and for those at risk, boosting is recommended every 3 years. The rapid vaccination schedules have shown similar efficacy in healthy individuals and are practical for travellers. Whether they are effective in HIV-infected persons is unknown. Only two published studies have investigated the immunogenicity of TBE vaccination in HIV-infected patients [216,217]. These studies suggest that the vaccine is less efficacious in HIV-infected individuals than in HIV-negative persons, particularly at CD4 counts <400–500 cells/μL. Although a four-dose vaccination schedule given at 0, 1, 2 and 9–12 months may improve responses in HIV-infected persons [218], evidence in support of this strategy remains limited [216]. The duration of protection in HIV-infected persons is unknown, but may be reduced compared to healthy individuals. However, there is insufficient evidence to guide a change in boosting recommendations.

A neutralizing antibody response >126 Vienna Units/mL is considered to be protective. Post-vaccination testing is not recommended routinely in healthy individuals, but may be considered in some immunocompromised persons. Information on TBE serological testing is available at the Special Pathogens Reference Unit (SPRU), HPA, Centre for Emergency Preparedness and Response, Porton Down, Salisbury, Wiltshire, SP4 0JG; tel: +44 1980 612 224; email: special.pathogens@hpa.org.uk; www.hpa.org.uk/srmd/other_ref_labs/spru.htm.

18.3.2 Vaccine safety

TBE vaccine is safe and well tolerated in HIV-infected individuals with CD4 count >200 cells/μL (216,217; H. Kollaritsch and M. Peallabauer, personal communications). Reported reactions are very rare. Injection site reactions are the most frequent side effects. Rarely, short-lived fever, vomiting or a temporary rash can occur. Very rarely arrhythmia and neurological disorders, including Guillain–Barré syndrome, have been reported. The vaccine has been suspected of causing an exacerbation of autoimmune diseases, but a cause-and-effect relationship has not been confirmed. Allergic reactions are uncommon in adults.

18.3.3 Contraindications

- Severe allergy to eggs.
- The vaccine may cause deterioration of some autoimmune conditions and a risk assessment should be made before administering the vaccine in these conditions.

18.4 Recommendations for TBE pre-exposure prophylaxis in HIV-infected adults

- The TBE vaccine should be considered for HIV-infected persons who intend to walk, camp or work in heavily forested regions of affected countries during late spring or summer when the ticks are most active, particularly if staying in areas with heavy undergrowth (C, IV). The vaccine is also recommended for expatriates whose principal area of residence is an area where TBE is endemic (C, IV).
- Three doses according to either the standard or the rapid vaccination schedule may be considered for persons with CD4 counts >400 cells/μL (C, IV).
- In individuals with CD4 counts <400 cells/μL, serological testing may be considered 1 month after the second vaccine dose (C, IV). In case of inadequate antibody response, two further vaccine doses should be given: one immediately and one 9–12 months after the first dose (C, IV). In the absence of serological testing, a four-dose vaccination schedule (0, 1, 2 and 9–12 months) should be adopted to improve response rates in this group (C, IV).

- Because of the possibility of reduced responses to vaccination, the importance of protective clothing and insect repellent use should be emphasized.
- A booster is recommended every 3 years for those at continued risk (C, IV).

18.5 Auditable outcomes

Offer TBE vaccination to HIV-infected patients who are at substantial risk of the infection (target 70%).

Complete vaccination course within 12 months of start (target 70% of those started on vaccine).

19.0 Typhoid fever

19.1 Background

Typhoid fever is caused by the gram-negative bacillus salmonella, serogroup typhi. Nearly 2000 salmonella serotypes are recognized, but most cause non-invasive infections of the gastrointestinal tract. *Salmonella typhi* is transmitted by the faecal–oral route through contaminated drinking water or food. Humans are the only reservoirs of the infection. Transplacental transmission can occur. *Salmonella typhi*, *Salmonella paratyphi A, B* and *C* and occasionally other salmonella species may cause invasive infections. Vaccination is only available against *S. typhi*.

The incubation period of typhoid fever is 5–21 days. Disease severity varies, but the infection can be life-threatening. Confusion, delirium, intestinal haemorrhage and perforation, and multi-organ involvement may occur. Untreated, the illness may last for 3–4 weeks, with a 12–30% risk of mortality. Antibiotic therapy leads to resolution of symptoms within 2–3 days, and death is rare in treated persons. Relapses may occur despite antibiotic therapy. About 10% of patients with typhoid fever excrete the organism for 3 months following the acute illness. A chronic carrier state, with excretion of *S. typhi* for more than 1 year, occurs in approximately 5% of infected persons.

19.2 Epidemiology and risk groups

Typhoid fever is common in the developing world. Between 12 and 33 million cases occur each year worldwide, with the highest incidence in Asia (especially the Indian sub-continent), Africa and Latin America; over 200 000 people die each year from the disease. Approximately 200 cases of infection with *S. typhi* are reported every year in the UK following travel to endemic areas or contacts with a carrier or a case, especially in family settings. Increasing resistance to available antibiotics, including fluoroquinolones, is reported. Multidrug-resistant strains of *S. typhi* have become common in the Indian sub-continent and the Middle East. Travellers to Asia, Africa and Latin America who have prolonged exposure to potentially contaminated food and drink are especially at risk of infection [218,219]. In these regions, the attack rate for travellers has been estimated at 10 per 100 000 travellers.

HIV-infected persons are at increased risk of infection with salmonella species and immunodeficiency predisposes patients to bacteraemia, antibiotic resistance, relapsing disease and persistent infection [220,221]. Disease manifestations among HIV-infected persons without severe immunodeficiency do not appear to differ significantly from those observed in HIV-negative persons, although increases in aspartate aminotransferase and abnormal urinary findings suggestive of glomerulonephritis may be more frequent in HIV-positive patients [222]. Patients with AIDS may present with more severe disease, including fulminant diarrhoea or colitis [220].

19.3 Typhoid vaccine

Three typhoid vaccines are available: (i) the parenteral ViCPS vaccine, containing purified Vi ('virulence') capsule polysaccharide; (ii) the oral Ty21a vaccine, containing live attenuated *S. typhi* Ty21a; and (iii) a whole-cell inactivated vaccine. A combined hepatitis A/ViCPS vaccine is also available [1,218,219]. The ViCPS vaccine is given intramuscularly (or subcutaneously in persons with bleeding disorders), preferably in the deltoid.

19.3.1 Vaccine efficacy

Typhoid vaccines are effective, but protection can be overwhelmed by large inocula of *S. typhi* [1,218,219]. One dose of the ViCPS vaccine induces antibodies in 93% of healthy adults [223,224]. Two trials in disease-endemic areas have demonstrated that the ViCPS vaccine is 49–87% effective in preventing laboratory-confirmed typhoid fever over a period of 2–3 years [225–234]. In a meta-analysis, the ViCPS vaccine provided protection for 2 years but the protection in the third year was not significant. In regions of low disease endemicity, the duration of protection is uncertain. For persons at risk, boosting is recommended every 3 years.

In HIV-infected persons, the induction of protective antibodies is directly correlated to the levels of CD4 cells. The antibody response in patients with CD4 counts <200 cells/μL is significantly lower compared to patients with higher CD4 cell counts and healthy controls [235]. The duration of protection may be reduced in HIV-infected persons.

19.3.2 Vaccine safety

The ViCPS vaccine is safe for HIV-infected persons. Injection site reactions, including swelling, redness or pain, have been reported in up to 7% of ViCPS recipients and usually resolve within 48 h. Systemic reactions such as headache and fever occur in up to 20% and 1% of vaccinees, respectively. Anaphylaxis and other serious adverse reactions are rare. The ViCPS vaccine is well tolerated in HIV-infected persons [235]. After vaccination with the Ty21a vaccine, transient shedding of vaccine organisms can occur, but secondary transmission of vaccine organisms to contacts has not been documented.

19.3.3 Contraindications

Although there have been no reports of adverse events associated with Ty21a vaccination in HIV-infected persons, the Ty21a vaccine is contraindicated in immunocompromised persons, including HIV-infected patients.

19.4 Recommendations for typhoid pre-exposure prophylaxis in HIV-infected adults

- Although not required for international travel, the ViCPS vaccine is recommended in all HIV-infected travellers to areas in which there is a recognized risk of exposure to *S. typhi* (C, IV). One dose of the vaccine should be given at least 2 weeks before expected exposure.
- Persons who will have intimate exposure (e.g. household contact) to a documented *S. typhi* carrier and laboratory workers exposed to *S. typhi* should also be offered vaccination (C, IV).
- A booster is recommended every 3 years in those who remain at risk. This interval might be reduced to 2 years if the CD4 count is <200 cells/μL (C, IV).
- Typhoid vaccines are not 100% protective and responses may be further reduced in HIV infection. Travellers should be advised to follow strict food and drink precautions.

19.5 Auditable outcomes

Number of at-risk individuals who are vaccinated (target 75%).

20.0 Tuberculosis

20.1 Background

The *Mycobacterium tuberculosis* complex includes *M. tuberculosis*, *M. bovis* and *M. africanum*. Transmission nearly always occurs through airborne droplets that are expelled when a person with pulmonary tuberculosis (TB) coughs, talks, sings or sneezes. The most infectious persons are those with cavitary pulmonary disease. Transmission usually requires prolonged exposure and close contact. In some cases transmission can also occur through unpasteurized milk or milk products from infected cattle.

The incubation period of TB ranges from weeks to years. Depending on host factors, infection may be cleared, remain latent or progress to active disease over a period of weeks or months. Disease is usually pulmonary (60% of cases), but non-pulmonary and disseminated disease can occur, especially in young children and immunocompromised persons, and almost every tissue and organ can be affected. Latent infection can re-activate. The lifetime risk of re-activation is 5–15% for immunocompetent adults. The majority of re-activations occur within 2 years of primary infection.

20.2 Epidemiology and risk groups

In the UK, cases of TB have increased over the last 10 years [1]. A large number of cases are in people born abroad, the rate being higher in certain ethnic groups in the first few years after they enter the country, and rates remain high in the children of these immigrants wherever they are born. The risk of infection is also increased in persons who are close contacts of infectious persons, have HIV infection, are homeless, abuse alcohol or inject drugs. Risk factors for disease are diabetes mellitus, renal failure, immunodeficiency, acquisition of latent infection in infancy or early childhood, and therapy with TNF-α antagonists [217]. The risk for active TB disease is high among HIV-infected persons: worldwide, TB is the leading cause of death among HIV-infected people. HIV also suppresses responses to the tuberculin test.

The mainstay of TB control is identifying and treating infectious cases to stop transmission, skin-testing children and adults who are at high risk for TB and (where indicated) administering preventive therapy to persons with a positive skin-test result [236]. Vaccination contributes to the prevention and control of TB in limited situations and is contraindicated in HIV infection.

20.3 Bacille Calmette–Guerin vaccine

The BCG vaccine is a live attenuated vaccine containing a strain of *M. bovis* isolated in 1908 from a cow, which was sub-cultured 231 times over 13 years resulting in gradual attenuation. Several laboratories produce vaccine derived from the original strain and many different BCG vaccines are available worldwide; these differ in their production

techniques and characteristics. BCG Vaccine Statens Serum Institut (SSI) is the only available licensed vaccine in the UK for administration intradermally in the later aspect of the left upper arm, using a multi-puncture device [1]. The vaccine is given as a single dose to selected high-risk infants and children, and previously unvaccinated tuberculin-negative close contacts of those with active respiratory TB [1]. The BCG vaccine is also indicated for previously unvaccinated tuberculin-negative adults below the age of 35 years if they are at occupational risk of exposure (e.g. healthcare workers, laboratory staff, veterinarians, prison staff, staff of care homes for the elderly, staff of hostels for homeless people and facilities accommodating refugees and asylum seekers) or intend to live or work in countries with an annual incidence of TB of 40/100 000 or greater. The BCG vaccine may also be considered for previously unvaccinated, tuberculin-negative individuals travelling to high-prevalence countries for 1 month or longer [1].

20.3.1 Vaccine efficacy

Studies of BCG vaccine are difficult to interpret because they differ in design, location, strains used, vaccine dose, population, presence of mycobacteria in the environment and diagnostic approach. Protection rates in different trials range between 9% and 80%. The BCG vaccine appears to prevent the blood-borne spread of *M. tuberculosis* from primary pulmonary foci, but the protection afforded against pulmonary disease is uncertain. A meta-analysis demonstrated 61–95% protection against meningitis and miliary disease in children [237]. Protective efficacy against pulmonary TB differed considerably between studies, precluding an estimation of the overall effect. A second meta-analysis showed an overall protective effect of 31–66% [238]. There remain limited data concerning the protective efficacy of vaccination in adults, but overall vaccine efficacy rates appear to be higher in persons vaccinated during childhood compared to persons vaccinated at older ages. There are virtually no data on vaccine efficacy in persons aged 35 years and over. Protection is thought to last for at least 10–15 years but data are limited. Repeat vaccination is not recommended. The protective efficacy of BCG vaccine in children and adults who are infected with HIV has not been determined.

20.3.2 Vaccine safety

The BCG vaccine often causes local adverse effects, but serious or long-term complications are rare in healthy individuals. Within 10–14 days, 90–95% of vaccine recipients develop an erythematous papule at the injection site, with induration and tenderness. It may ulcerate and then slowly subside over several weeks or months to heal leaving a small, flat scar of 5–15 mm in diameter. There may be enlargement of a regional lymph node to <1 cm [1]. Severe injection site reactions may occur, usually as a result of faulty injection technique, excessive dosage or vaccinating individuals who are tuberculin-positive. Other adverse reactions to the vaccine include headache, fever, lymphadenopathy >1 cm, allergic reactions (including anaphylactic reactions) and, rarely, lymphadenitis and disseminated BCG complications (such as osteitis or osteomyelitis) [1].

Fatal dissemination has been described in immunocompromised individuals. Case reports indicate that symptomatic HIV-infected persons are at greater risk for local ulceration, lymphadenitis, disseminated BCG disease and other complications from BCG vaccine than HIV-negative persons or persons with asymptomatic HIV infection [239–245]. Disseminated BCG disease after vaccination has occurred in at least one child and one adult who were infected with HIV [246]. These complications can occur several years after BCG vaccination. However, studies in Zaire, Haiti and Congo did not demonstrate an association between HIV seropositivity and adverse responses to BCG vaccination [247,248].

20.3.3 Contraindications

- The BCG vaccine is contraindicated in all patients who are immunocompromised as a result of disease or treatment, including HIV-infected persons.
- The vaccine should not be used in pregnancy unless there is an overriding reason to offer vaccination.
- No further immunization should be given in the arm used for BCG immunization for at least 3 months because of the risk of regional lymphadenitis.
- Other contraindications include: past history of TB, induration of 6 mm or more following Mantoux tuberculin skin testing, confirmed anaphylactic reaction to a component of the vaccine, neonates in a household where an active TB case is suspected or confirmed.
- Where BCG vaccination is indicated in infants born to HIV-positive mothers, it should be administered only after two appropriately timed, negative post-natal polymerase chain reaction (PCR)-based HIV tests.

20.4 Recommendations for TB pre-exposure prophylaxis in HIV-infected adults

- Until the risk–benefit of BCG vaccination in HIV-infected adults is established, the vaccine is absolutely contraindicated in all HIV-positive persons regardless of CD4 cell count and clinical status (C, IV).

- BCG is also contraindicated in persons suspected to be HIV-positive, regardless of clinical status (C, IV).

20.5 Auditable outcomes

Record history of childhood or other BCG vaccination in newly diagnosed HIV-infected persons (target 95%).

21.0 Varicella zoster virus

21.1 Background

Varicella zoster virus (VZV) is a member of the herpes virus family. Primary infection typically causes varicella (chickenpox). Subsequent reactivation of latent infection causes zoster (shingles). Varicella is highly infectious and can be transmitted by the respiratory route up to 48 h prior to onset of the rash. The skin lesions of varicella and zoster are considered to be infectious until crusted over (usually 7 days). Healing can be slow in immunocompromised persons, who may remain infectious for several weeks.

The incubation period of varicella is 10–21 days. Varicella is characterized by a generalized vesicular rash. Whereas immunocompetent children usually have benign and self-limiting disease, adults are more likely to develop severe varicella leading to hospitalization and death. Complications of varicella include severe cutaneous disease, secondary bacterial infection of skin lesions, visceral involvement (e.g. pneumonia, hepatitis) and neurological disease. All adults with varicella are at risk for varicella pneumonia; the risk is especially high in pregnant women. Occasionally, infection in pregnancy leads to foetal injury (congenital varicella syndrome).

Zoster is a self-limiting, painful, localized vesicular rash occurring over one to three unilateral contiguous dermatomes in the normal host. Pain is a frequent complication of zoster and may persist after resolution of the rash (postherpetic neuralgia). Cutaneous dissemination or visceral involvement may occur in individuals with compromised immunity.

21.2 Epidemiology and risk groups

In temperate climates, primary infection with VZV occurs most commonly during childhood. At least 90% of adults in England and Wales are VZV IgG seropositive [249], confirming prior infection. In tropical and sub-tropical climates, the mean age of primary VZV infection may be delayed. As a result, a significant proportion of adults raised in those regions remain VZV IgG seronegative and susceptible to primary infection in adulthood [250,251]. Zoster is common in immunocompetent individuals with an overall rate of 373 per 100 000 population years [252].

Patients with HIV infection are at risk of developing severe illness from either varicella or zoster. Patients with varicella are at risk for severe or disseminated cutaneous disease, secondary bacterial infection of skin lesions and visceral involvement. Progressive primary varicella, a syndrome with persistent new lesion formation and visceral dissemination, may be life-threatening. In the pre-highly active antiretroviral therapy (HAART) era, approximately 25% of in-patients with varicella developed severe complications including haemorrhagic rash, pneumonitis and fulminant infection with disseminated intravascular coagulation [251].

HIV-infected persons have a higher frequency of zoster than the general population. Although most have an uncomplicated clinical course, patients are prone to complications including multidermatomal, disseminated and chronic atypical skin rashes [253]. Acute retinal necrosis and neurological syndromes including encephalitis, myelitis and meningitis can occur in the absence of rash. Zoster continues to be common in the era of HAART and has been recognized as a manifestation of immunoreconstitution disease [254].

21.3 VZV vaccine

The VZV vaccine contains live attenuated virus propagated in human diploid cells. Two vaccines are available based on the OKA strain (Varilrix) or the OKA/Merck strain (Varivax). The vaccine can establish latent infection in some vaccinees and reactivate to cause zoster. However, this occurs less often than with wild-type virus. In the UK, the varicella vaccine is currently recommended for susceptible healthcare workers and healthy contacts of immunocompromised patients [1]. The vaccine is administered by subcutaneous injection, preferably in the deltoid.

21.3.1 Vaccine efficacy

In immunocompetent adults, two doses of varicella vaccine give 75% protection against any disease and >95% protection against severe disease [1]. Waning immunity over time is manifested by mild breakthrough infections with wild-type virus. Vaccinated healthcare workers followed for up to 8 years have an attack rate of 10% [255]. The need for booster doses is currently under investigation. Vaccination of VZV IgG seropositive immunocompetent adults with a high dose of the VZV vaccine to boost natural immunity has recently been shown to halve the incidence of herpes zoster and to reduce

the frequency of post-herpetic neuralgia by two thirds [256].

The VZV vaccine has been shown to be immunogenic in susceptible children with asymptomatic or mildly symptomatic HIV infection [257]. After two doses, 60% seroconverted for VZV IgG and 83% showed T-cell proliferative responses. Consideration of vaccination has been recommended for this group [253,258]. In a more recent vaccine study, VZV-susceptible children with moderate symptoms and/or more pronounced past or current decreases in CD4 cell counts received two doses, 3 months apart [259]. The vaccine was well tolerated and effective, with VZV-specific immune responses detectable in over 80% of vaccinees 1 year following vaccination. As a result, consideration of varicella vaccination has recently been extended to include these groups [258].

There are limited data on the efficacy of vaccination among HIV-infected adults. Among VZV IgG seropositive persons with nadir CD4 counts >400 cells/μL and stable on antiretroviral therapy (ART) for at least 3 months, the vaccine has been shown to boost VZV-specific cellular immune responses. Less robust responses have been observed in patients with a nadir CD4 count <200 cells/μL restored to >400 cells/μL with HAART [260]. By extrapolation of the recent observations in children, expert opinion in the USA now advises consideration of VZV vaccination in older children and adults with CD4 counts >200 cells/μL [258,261].

21.3.2 Vaccine safety

Up to 10% of immunocompetent adults develop a vaccine-associated rash, localized at the site of injection or generalized, within 1 month of immunization [262,263]. Severe but non-fatal varicella vaccine-associated disease has been reported in some children with undiagnosed immunodeficiency [264]. Overall, however, the vaccine is regarded as safe in children with asymptomatic or minimally symptomatic HIV infection and an age-specific CD4 cell count $\geq 15\%$ [261]. In VZV IgG seropositive HIV-infected adults with CD4 counts >400 cells/μL while on HAART no excess adverse events have been reported following VZV vaccination [260]. The vaccine strain is sensitive to antiviral therapy with aciclovir.

Transmission of vaccine virus from vaccinees has been documented only rarely and only from individuals with vaccine-associated rashes. Vaccination is not contraindicated and is in fact recommended for close contacts of HIV-infected persons. Post-vaccine rashes may be investigated to determine whether they are caused by wild type or vaccine virus. Information on testing is available from the HPA Varicella Reference Service (www.clinical-virology.org/pages/vzrl/vzrl_summary.html).

21.3.3 Contraindication

- Pregnancy and breast feeding.
- Significant immunodeficiency [1].

21.4 Recommendations for varicella pre-exposure prophylaxis in HIV-infected adults

- Because HIV-infected persons are at increased risk for morbidity from varicella and zoster compared to healthy persons, vaccination of susceptible adults who have no evidence of significant immunodeficiency may be a useful strategy to prevent both varicella and zoster in this population (C, IV).
- HIV-infected adults with a negative or uncertain history of varicella or zoster should be tested for VZV IgG (C, IV).
- After weighing potential risks and benefits, vaccination is recommended for VZV IgG seronegative asymptomatic HIV-infected adults with a CD4 count >400 cells/μL (C, IV).
- Vaccination may also be considered for VZV IgG seronegative asymptomatic HIV-infected patients with CD4 counts <400 cells/μL but >200 cells/μL while on stable HAART (C, IV).
- Two vaccine doses are recommended. A 3-month interval is recommended between doses (C, IV).
- Vaccinees should be warned to report post-vaccine rashes or other symptoms and be evaluated promptly for antiviral therapy. Patients who develop a post-vaccine rash or other adverse effects should receive prompt medical evaluation and antiviral therapy for VZV (C, IV). The HPA can be contacted for advice (www.clinical-virology.org/pages/vzrl/vzrl_summary.html).
- Serological evidence to demonstrate VZV IgG seroconversion should be performed 4–6 weeks after the second vaccine dose (C, IV).
- The VZV vaccine is also recommended for susceptible close contacts of HIV-infected adults because the risk of transmission of the vaccine virus is significantly less than the risk of transmission of varicella.

21.5 Post-exposure prophylaxis

Protective immunity develops within 4 days of VZV vaccination, and Varivax (but not Varilrix) is licensed for post-exposure prophylaxis in susceptible individuals exposed to VZV. The vaccine should be administered within 3 days of exposure. The manufacturers quote limited data supporting its use up to 5 days post-exposure [265]. Available evidence supports post-exposure prophylaxis

with the VZV vaccine in healthy individuals [266]. However, protection is <100%: mild cases of infectious chickenpox occur, especially after household exposure. There are currently no data supporting this strategy in HIV infection. The risk of vaccine-related adverse events must be balanced against the risk of severe complications resulting from natural infection in these patients.

Varicella-zoster immunoglobulin (VZIG), made from pooled plasma of non-UK donors with suitably high titres of VZV antibody, is indicated for susceptible immunocompromised patients and pregnant women who have had a significant exposure to VZV. This includes symptomatic HIV-positive patients and asymptomatic patients with CD4 count <400 cells/μL [1]. VZIG is given by intramuscular injection.

The standard adult dose (1000 mg) should be administered within 10 days and, ideally, within 7 days of exposure. The duration of protection is 3 weeks. In the event of a second exposure after 3 weeks, repeat administration of VZIG prophylaxis is recommended [1]. Rare anaphylactic reactions have occurred in individuals with hypo-gammaglobulinaemia or prior blood transfusion reactions. VZV antibody negative, immunosuppressed home contacts given VZIG within 10 days of exposure have a clinical attack rate of 54%. A further 15% become infected sub-clinically. By comparison with the expected 90% case rate in unprotected household contacts, VZIG has a protective efficacy of 40% [267]. There is no published evidence of VZIG efficacy in HIV-infected patients. Where intramuscular injection is contraindicated in individuals with bleeding disorders, intravenous immunoglobulin (0.2 g/kg body weight) may be given instead.

Limited data indicate that varicella may be prevented or attenuated in healthy children by administration of aciclovir starting between 7 and 10 days after exposure, for a total of 7 days [268,269]. The equivalent dose of aciclovir in adults is 800 mg four times daily. There are no published controlled trials comparing aciclovir prophylaxis directly with VZIG.

21.6 Recommendations for varicella post-exposure prophylaxis in HIV-infected adults

- Following a significant exposure to varicella or zoster, the VZV IgG status should be ascertained but prophylaxis should not be delayed waiting for the results.
- VZV IgG seronegative patients should be considered for post-exposure prophylaxis and monitored closely for symptoms of varicella to facilitate prompt institution of antiviral therapy.
- Post-exposure prophylaxis should be tailored to the patient's clinical status and the following approach is recommended:

Symptomatic HIV infection and/or CD4 counts <400 cells/μL (with or without HAART) (C, IV):
- VZIG must be given as soon as possible, preferably within 7 days and not later than 10 days after exposure.
- Antiviral chemoprophylaxis with oral aciclovir (800 mg four times daily or equivalent) for 7 days, commencing 7–10 days post-exposure, may be considered if VZIG is not available, or given in conjunction with VZIG in profoundly immunocompromised patients.

Asymptomatic HIV infection and CD4 counts >400 cells/μL (with or without HAART) (C, IV):
- Vaccination with Varivax should be considered within 3 days of exposure. The second dose should normally be scheduled after 3 months, with subsequent serological testing to confirm VZV IgG seroconversion 4–6 weeks after the second vaccine dose.

21.7 Auditable outcomes

1. Determine the VZV susceptibility status of HIV-infected patients with a significant exposure to varicella or zoster (target 100%).
2. Offer VZV screening and subsequent varicella vaccination to VZV IgG seronegative household contacts of severely immunocompromised HIV patients (target 80%).

22.0 Yellow fever

22.1 Background

The yellow fever virus (YFV) is a flavivirus transmitted from monkey to monkey, monkey to man, and man to man predominantly by *Aedes aegypti* mosquitoes. The incubation period of yellow fever is 3–6 days. The severity of infection varies from an influenza-like illness to severe hepatitis and haemorrhagic fever. The more severe forms have a mortality of up to 50% in non-immune adults travelling to endemic areas [270]. There is no antiviral or other effective therapy.

22.2 Epidemiology and risk groups

YFV is prevalent in tropical and sub-tropical regions of Africa and South America, where it is endemic and

intermittently epidemic. It does not occur in Asia. Two forms of yellow fever – urban and jungle – are epidemiologically distinguishable. In South America, sporadic infections occur almost exclusively as a result of occupational exposure in or near forested areas. In Africa, the virus is transmitted mainly in the moist savannah zones of west-central Africa, especially during the late rainy and early dry season (July–October). For travellers to endemic areas the risk of acquiring yellow fever has been estimated to be 0.4–4.3 cases per million travellers [271]. The risk of disease is around 10 times lower in South America than in rural west Africa, but varies greatly according to specific location and season. Vaccination, along with an International Certificate of Vaccination, is compulsory for entry to several countries in these regions. The International Certificate is valid for 10 years from the tenth day after primary vaccination and immediately after revaccination.

There are no data to indicate whether the natural history of yellow fever is modified by HIV infection.

22.3 YFV vaccine

In the UK two products (Stamaril and Arilvax) are available, each consisting of a live attenuated preparation of the 17D strain of YFV grown in chick embryos. Vaccination can only be given at designated centres competent in yellow fever vaccination in the UK [1]. The YFV is given as a single dose by subcutaneous injection, preferably in the deltoid.

22.3.1 Vaccine efficacy

A single dose of the YFV vaccine has a protective efficacy of 90% after 10 days and 99% after 30 days [1]. The protection lasts for at least 10 years (for which duration the certificate of vaccination is valid), after which a booster is required for those at continued risk. However, evidence from multiple studies demonstrates that immunity persists for 30–35 years and probably for life.

Data in HIV-infected persons are limited. Although development of neutralizing antibodies may be reduced [272,273], high seroconversion rates (around 70%) have been observed in HIV-infected adults with CD4 counts >200 cells/μL, most of whom where on highly active antiretroviral therapy (HAART) at the time of vaccination [274]. The duration of protection in HIV-infected persons is unknown, but may be reduced compared to HIV-negative persons.

22.3.2 Vaccine safety

Injection site reactions are the most common adverse events reported. An influenza-like illness occurs in 2–10% of vaccine recipients 5–14 days after immunization. More serious adverse events are very rare and less common in those who have had previous immunization. These are principally hypersensitivity or anaphylaxis (one per 130 000–250 000), neurotropic disease (one per 250 000–8 million) and the recently recognized viscerotropic disease (one per 40 000–1 200 000) [275,276]. The latter two complications have been increasingly recognized in older recipients, with a combined incidence of one per 25 000 and one per 13 000 for those in the 60–69 and ≥ 70 years age groups, respectively [275]. The viscerotropic disease is characterized by multi-organ involvement and 50% risk of mortality. It resembles naturally acquired yellow fever clinically and pathologically. A history of thymic dysfunction may be a risk factor.

These data have led to many older travellers being advised not to undergo vaccination and instead receive a certificate of exemption when absolute risks of infection are low. Studies are being conducted to clarify the cause and risk factors for these rare adverse events associated with the YFV vaccines.

Over recent years there have been an increasing number of reports suggesting that vaccination may be safe in HIV-infected adults with less advanced disease. Recent data provide cautious support for the safety and efficacy of YFV vaccination in HIV-infected patients with CD4 counts >200 cells/μL, either in early HIV infection or following HAART [272–274, 277]. There has been only one published case of fatal encephalomyelitis after receiving this vaccine, in a Thai man with asymptomatic infection and a CD4 count of 108 cells/μL [278].

22.3.3 Contraindications

There are three groups of adult people who should not receive the vaccine unless the risk of yellow fever exceeds the small risk associated with the vaccine. The following people should either obtain a waiver letter prior to travel or delay travel to an area with active yellow fever transmission:

- People with severe egg allergy.
- Pregnant women and breast feeding mothers.
- Persons with immunodeficiency caused by disease or treatment. Current UK Department of Health recommendations for YFV vaccination exclude those with HIV infection at all stages [1], while the American Advisory Committee on Immunization Practices (ACIP) recommends that it may be given to those with a CD4 count >200 cells/μL travelling to high-risk areas [277].

22.4 Recommendations for yellow fever pre-exposure prophylaxis in HIV-infected adults

- Asymptomatic HIV-infected persons with CD4 counts >200 cells/μL who are due to travel to countries in which there is a risk of exposure to YFV infection should be offered the choice of vaccination, after appropriate counselling of the risks (B, III).
- Vaccination should be undertaken at least 2 weeks before travel and vaccine recipients should be monitored closely after vaccination (C, IV).
- Physicians should be careful to administer the vaccine only to persons truly at risk for exposure. If international travel requirements and not true exposure risk are the only reasons to vaccinate, a certificate of exemption should be given (C, IV).
- HIV-infected adults with CD4 counts <200 cells/μL or over 60 years of age should not receive vaccination until more data are available on vaccine safety in these groups (BIII). They should be strongly discouraged from travel to destinations that present a true risk of infection.
- Travellers should be warned that vaccination waiver documents may not be accepted by some countries and that if the waiver is rejected, the option of deportation might be preferable to YFV vaccination (C, IV).
- The importance of precautions against mosquito bites should be emphasized.
- The YFV is given as a single dose. A booster is indicated after 10 years for those at risk, provided the CD4 count is >200 cells/μL (C, IV). A serological test should precede vaccination and guide boosting requirements in those at greater risk of side effects (C, IV).

22.5 Auditable outcomes

Proportion of at-risk HIV-infected individuals who receive advice about yellow fever vaccination prior to travel to endemic areas (target 90%).

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Appendix 1: useful links

- Children's HIV Association: www.bhiva.org/chiva/
- Health Protection Agency: www.hpa.org.uk
- Centers for Disease Control and Prevention: www.cdc.gov/
- World Health Organization: www.who.int/en/
- National Travel Health Network and Centre: www.nathnac.org/pro/index.htm