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Dr Anna Maria Geretti
Introduction

a. Statement of intent
Routine immunisation against infectious diseases is primarily directed towards children and adolescents and it is not commonplace in adult practice. However adults in general and HIV-infected persons in particular may experience considerable morbidity and mortality due to vaccine-preventable diseases. These guidelines contain evidence-graded recommendations that can assist clinicians in making decisions on the appropriate use of active and passive immunisation in HIV-infected adults. Their primary objective is to inform clinical practice based on the best available evidence and expert consensus opinion at the time of development. Background information on vaccine-preventable diseases and immunisation strategies in the general population provide the context for discussion of HIV-related issues. Key references are given at the end of each chapter.

Whenever possible the guidelines have been kept consistent with recommendations from the Department of Health (Immunisation Against Infectious Disease - "The Green Book"*), which are complemented by this guidance.


These guidelines address immunisation issues concerning adults (age above 16 years) infected with HIV-1. The reader is referred to guidelines issued by the Children’s HIV Association (CHIVA*) for recommendations concerning children and adolescents.

* available at: http://www.bhiva.org/chiva/

b. The review process
Each guideline was prepared by one or two authors and reviewed and approved by the Writing Committee. In cases when opinions were divided and for the more complex aspects of the guidelines, guidance was sought from external reviewers. There is a paucity of controlled studies that can be relied upon to inform the formulation of immunisation guidelines in HIV-infected adults. As a result, the recommendations are often expression of a consensus derived from descriptive studies, clinical experience and expert opinion. Available published evidence was derived from peer-reviewed studies and from abstracts presented at international conferences in the last three years. In addition, the following sources of information were consulted: The Health Protection Agency website at http://www.hpa.org.uk; The USA Centers for Disease Control and Prevention (CDC) website at http://www.cdc.gov/; the World Health Organisation (WHO) website at http://www.who.int/en/.
The recommendations on pneumococcus vaccination are tentative, due to the contradictory evidence on safety and efficacy of the polysaccharide vaccine. Further expert advice is being sought and feedback is encouraged on this and all other topics addressed by the guidelines.

The current draft is the product of a complex development and consultation process. It is anticipated that revision will be required as new vaccines are introduced, more evidence becomes available, clinical experience increases, and understanding of the immune-restorative effects of antiretroviral therapy improves. The draft will be revised in October 2006 following a period of wide consultation. Subsequent revisions will be made every two years or sooner if new evidence becomes available. Feedback on any aspect of the guidelines is welcome and encouraged.

c. Level of evidence and grading of recommendations

Level of evidence
- Ia evidence obtained from meta-analysis of randomised controlled trials
- Ib evidence obtained from at least one randomised controlled trial
- IIa evidence obtained from at least one well designed controlled study without randomisation
- IIb evidence obtained from at least one other type of well designed quasi-experimental study
- III evidence obtained from well designed non-experimental descriptive studies
- IV evidence obtained from expert committee reports or opinions and/or clinical experience 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

d. The rationale for issuing HIV-specific immunisation guidelines

There are several factors that make the formulation of HIV-specific immunisation guidelines important, at a time when vaccination practices are changing (e.g., reintroduction of smallpox vaccination for selected health care workers as a response to the threat of bioterrorism), new vaccines are being introduced (e.g., intranasal live influenza vaccine), and the natural history of HIV infection is being modified by highly active antiretroviral therapy (HAART). Compared with HIV-seronegative individuals, HIV-seropositive persons may have an increased risk of infection or experience more severe disease following exposure to vaccine-preventable diseases. In some cases behavioural characteristics may increase the risk of exposure to certain infections (e.g., hepatitis A in homosexual men). In other cases, compromised immunity alters the risk of serious consequences of the infection (e.g., increased risk of chronicity following infection with hepatitis B), lowering the threshold for recommending immunisation.
Reduced responses to vaccination are common in HIV-infected persons, who may therefore require additional vaccine doses and modified schedules. Furthermore, reduced rates and durability of responses may require more frequent use of serological testing to assess levels of protection and guide boosting requirements than recommended in HIV-seronegative persons (e.g., in rabies post-exposure prophylaxis).

Safety of vaccination is an important consideration. In some cases, the increased risk of adverse reactions either contraindicates the use of certain vaccines or restricts them to HIV-infected persons with good immune function. Traditionally the use of live vaccines has been contraindicated in HIV-infected persons. However, the immune reconstitution induced by HAART is likely 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 cautiously used in HIV-infected persons with good immune status include those against measles, mumps and rubella (MMR), varicella and yellow fever. Other live vaccines remain contraindicated, either because safe inactivated alternatives are available (e.g., typhoid), or due to lack of safety data and uncertainty about the magnitude of vaccine efficacy (e.g., BCG).

One additional consideration is that a significant proportion of HIV-infected persons may have migrated to the UK in adult life and perhaps missed vaccinations that are part of the routine childhood schedule. Current national guidelines recommend that efforts should be made to offer vaccination to adults who remain susceptible to disease such as tetanus or poliomyelitis. Finally, as a result of improved health and prognosis, many HIV-infected persons are likely to engage in exposure-prone activities, either as a result of occupation or because of travel, and may require vaccines that are traditionally contraindicated in immunocompromised persons, but may be safe to use in HIV-infected persons with restored immunity. Guidance is required to manage these new scenarios and it is hoped that the availability of clear and up-to-date immunisation guidelines will facilitate the process.

e. General principles of immunisation in HIV-infected adults

- Persons with symptomatic HIV infection or CD4 counts <200 cells/mm$^3$ must not be given live vaccines. Where appropriate, vaccination should be reconsidered following immune restoration.

- Household and other close contacts of severely immunocompromised HIV-infected patients should not be given the transmissible oral polio vaccine or the intranasal influenza vaccine, but can be given vaccines against measles, mumps and rubella (MMR), varicella and yellow fever (see specific guidance about the smallpox vaccine, Chapter IV.o).

- Asymptomatic HIV-infected persons with CD4 counts above 400-500 cells/mm$^3$ are generally regarded as sufficiently immunocompetent, whereas those with CD4 counts
between 200 and 400-500 cells/mm$^3$ are considered to be immunocompromised to a limited degree. An important source of complexity is related to the degree of immunoreconstitution induced by antiretroviral therapy in persons with previous symptomatic disease and low nadir CD4 counts. In keeping with consensus opinion and clinical experience, these guidelines recommend that the current CD4 count rather than the nadir should be used to categorise HIV-infected persons. However, it should be acknowledged that generalisations about immune function are difficult, given that the exact timing and extent of HAART-induced immunoreconstitution have not been well defined for most vaccine-preventable diseases. It is recommended that stable immunoreconstitution should be documented in order to optimise vaccine responses and minimise possible risks. As a general rule, a wait of 3 months post-reconstitution before immunization is generally recommended. Clinical judgement should be used to estimate the degree of immunocompetence of individual patients.

- The following groups of individuals should not receive live vaccines regardless of CD4 count:
  - Patients receiving systemic steroids or other immunosuppressive therapy or within 3 months of terminating such treatment.
  - Patients with lymphoma, leukaemia or other haematological malignancies.
  - Patients being treated for malignancy with chemotherapy or generalised radiotherapy, or within 6 months of terminating such treatment.

- As per standard recommendations, live vaccines (with the exception of yellow fever vaccine) should not be given within the three months following injection of immunoglobulin.

- Live vaccines can be administered simultaneously with other live or inactivated vaccines, using different sites. If not given simultaneously, live vaccines should be administered with an interval of three weeks between each vaccine.

- When multiple vaccines are given at the same time, a separate site should be used. If the vaccines must be given in the same limb, they should be given at least 2.5 cm apart.

- The level and duration of vaccine-induced protection are often reduced in HIV-infected persons. In some cases there exists evidence supporting the use of higher or more frequent vaccine doses to improve response rates. In patients with CD4 counts <200 cells/mm$^3$, depending on the level of risk, consideration should be given to either delaying immunisation or repeating immunisation following HAART-induced immunoreconstitution (CD4 >400-500 cells/mm$^3$). It should be noted however that responses to vaccination can be observed in a substantial proportion of patients with CD4 counts <200 cells/mm$^3$. The potential benefit of immunisation should not therefore be denied to persons with low CD4 counts based upon the anticipated reduced immunogenicity, provided the vaccine is safe at low CD4 counts.
• 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 a HIV-infected person, if the risk of infection is significant.

• Transient increases in plasma HIV RNA load have been reported after administration of several vaccines to HIV-infected persons. Available evidence indicates that these transient increases do not have clinical significance and should not preclude the use of any vaccine.

f. Practical considerations
It is hoped that these guidelines will assist the judicious use of vaccines as a cost-effective way of reducing the burden of morbidity and mortality due to vaccine-preventable diseases among HIV-infected adults, while also providing a wider public health benefit. It is recognised that the responsibility for providing recommended immunisations and 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. Feedback on this issue is encouraged.

g. Links
• Department of Health. Immunisation Against Infectious Diseases – “Green Book”
• Children’s HIV Association: http://www.bhiva.org/chiva/
• Health Protection Agency: http://www.hpa.org.uk
• USA Centers for Disease Control and Prevention: http://www.cdc.gov/
• World Health Organisation: http://www.who.int/en/
• National Travel Health Network & Centre: http://www.nathnac.org/pro/index.htm
Table 1. Vaccines contraindicated in all HIV-infected adults

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Type</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholera CVD103-HgR</td>
<td>Live</td>
<td></td>
</tr>
<tr>
<td>Influenza-intranasal</td>
<td>Live</td>
<td>Also contraindicated in close contacts</td>
</tr>
<tr>
<td>Poliomyelitis-oral (OPV)</td>
<td>Live</td>
<td>Also contraindicated in close contacts</td>
</tr>
<tr>
<td>Typhoid-Ty21a</td>
<td>Live</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis (BCG)</td>
<td>Live</td>
<td></td>
</tr>
<tr>
<td>Smallpox (Vaccinia)</td>
<td>Live</td>
<td>See notes about patients and contacts</td>
</tr>
</tbody>
</table>

Table 2. Vaccines that can be used in HIV-infected adults regardless of CD4 count

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Type</th>
<th>Indication*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax</td>
<td>Inactivated</td>
<td>RS</td>
</tr>
<tr>
<td>Cholera-WC/rBS</td>
<td>Inactivated</td>
<td>RS</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Inactivated</td>
<td>RS</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Inactivated</td>
<td>R</td>
</tr>
<tr>
<td>Haemophilus influenza B (Hib)</td>
<td>Inactivated</td>
<td>RS</td>
</tr>
<tr>
<td>Influenza-parenteral</td>
<td>Inactivated</td>
<td>R</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Inactivated</td>
<td>RS</td>
</tr>
<tr>
<td>Meningococcus-MenC</td>
<td>Inactivated</td>
<td>RS</td>
</tr>
<tr>
<td>Meningococcus-ACWY</td>
<td>Inactivated</td>
<td>RS</td>
</tr>
<tr>
<td>Pneumococcus-PPV23</td>
<td>Inactivated</td>
<td>R/CS</td>
</tr>
<tr>
<td>Poliomyelitis-parenteral (IPV)</td>
<td>Inactivated</td>
<td>RS</td>
</tr>
<tr>
<td>Rabies</td>
<td>Inactivated</td>
<td>RS</td>
</tr>
<tr>
<td>Tetanus-Diphtheria (Td)</td>
<td>Inactivated</td>
<td>RS</td>
</tr>
<tr>
<td>Tick borne encephalitis</td>
<td>Inactivated</td>
<td>RS</td>
</tr>
<tr>
<td>Typhoid-ViCPS</td>
<td>Inactivated</td>
<td>RS</td>
</tr>
</tbody>
</table>

R=Recommended; RS= Recommended in selected groups; CS= May be considered in selected groups

* Please refer to relevant chapters for the specific indications

Table 3. Vaccines that should be administered to HIV-infected adults only if they are asymptomatic with a current CD4 count >200 cells/mm³

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Type</th>
<th>Indication*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles, Mumps, Rubella (MMR)</td>
<td>Live</td>
<td>RS</td>
</tr>
<tr>
<td>Varicella</td>
<td>Live</td>
<td>RS/CS</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>Live</td>
<td>CS</td>
</tr>
</tbody>
</table>

RS= Recommended in selected groups; CS= May be considered in selected groups

* Please refer to relevant chapters for the specific indications
## Table 4. Schedule for pre-exposure vaccination in HIV-infected adults

<table>
<thead>
<tr>
<th>Indication</th>
<th>Current CD4 count (cells/mm³)</th>
<th>Primary course</th>
<th>Boosting</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax</td>
<td>RS Any</td>
<td>4 doses</td>
<td>Yearly</td>
<td></td>
</tr>
<tr>
<td>Cholera-WC/rBS</td>
<td>RS Any</td>
<td>2 doses</td>
<td>2 years</td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>RS Any</td>
<td>2 or 3 doses</td>
<td>5 years</td>
<td>3 doses if CD4 &lt;300</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>R Any</td>
<td>3 or 4 doses</td>
<td>HBsAb &lt;100 IU/L</td>
<td>HBsAb levels yearly</td>
</tr>
<tr>
<td>Haemophilus influenzae (Hib)</td>
<td>RS Any</td>
<td>Single dose</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Influenza-parenteral</td>
<td>R Any</td>
<td>Single dose</td>
<td>Repeat yearly</td>
<td></td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>RS Any</td>
<td>3 or 4 doses</td>
<td>3 years</td>
<td>4 doses if age &gt;60</td>
</tr>
<tr>
<td>Measles, Mumps, Rubella (MMR)</td>
<td>RS &gt;200</td>
<td>1 or 2 doses</td>
<td>None</td>
<td>2 doses if asplenia or splenic dysfunction</td>
</tr>
<tr>
<td>Meningococcus-MenC</td>
<td>RS Any</td>
<td>1 or 2 doses</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Meningococcus-ACWY</td>
<td>RS Any</td>
<td>Single dose</td>
<td>5 years</td>
<td></td>
</tr>
<tr>
<td>Pneumococcus-PPV23</td>
<td>R/CS R= &gt;200 CS= &lt;200</td>
<td>Single dose</td>
<td>Generally none</td>
<td>Consider boost after 5-10 years</td>
</tr>
<tr>
<td>Poliomyelitis-parenteral (IPV)</td>
<td>RS Any</td>
<td>1 to 5 doses</td>
<td>10 years</td>
<td></td>
</tr>
<tr>
<td>Rabies</td>
<td>RS Any</td>
<td>3 doses</td>
<td>1 (first) or 3-5 years (subsequent)</td>
<td></td>
</tr>
<tr>
<td>Tetanus-Diphtheria (Td)</td>
<td>RS Any</td>
<td>1 to 5 doses</td>
<td>10 years</td>
<td></td>
</tr>
<tr>
<td>Tick borne encephalitis</td>
<td>RS Any</td>
<td>3 or 4 doses</td>
<td>3 years</td>
<td>4 doses if CD4 &lt;400</td>
</tr>
<tr>
<td>Typhoid-ViCPS</td>
<td>RS Any</td>
<td>Single dose</td>
<td>2-3 years</td>
<td>Boost after 2 years if CD4 &lt;200</td>
</tr>
<tr>
<td>Varicella</td>
<td>RS/CS RS= &gt;400; CS= &gt;200</td>
<td>2 doses</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>CS &gt;200</td>
<td>Single dose</td>
<td>10 years</td>
<td>Contraindicated if age &gt;60</td>
</tr>
</tbody>
</table>

R=Recommended; RS= Recommended in selected groups; CS= May be considered in selected groups

* Please refer to relevant chapters for the specific indications
Table 5. Vaccines recommended for all susceptible HIV-infected adults*  

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Current CD4 count (cells/mm$^3$)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Influenza-parenteral</td>
<td>Any</td>
<td>The indications for vaccination are strengthened in the presence of additional risk factors</td>
</tr>
<tr>
<td>Pneumococcus- PPV23</td>
<td>R= &gt;200 CS= &lt;200</td>
<td>The indications for vaccination are strengthened in the presence of additional risk factors</td>
</tr>
<tr>
<td>Varicella</td>
<td>CS= &lt;400 and &gt;200</td>
<td>May also be considered for post-exposure prophylaxis</td>
</tr>
</tbody>
</table>

R=Recommended; CS= May be considered in selected groups  
* Please refer to relevant chapters for the specific indications

Table 6. Vaccines recommended for HIV-infected adults who have missed routine childhood vaccinations or have uncertain vaccination history*  

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Group</th>
<th>Current CD4 (cells/mm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus-Diphtheria/Polioyelitis-Parenteral (Td/IPV)</td>
<td>All</td>
<td>Any</td>
</tr>
<tr>
<td>Meningococcus-MenC</td>
<td>Adults &lt;25 years</td>
<td>Any</td>
</tr>
<tr>
<td>Measles, Mumps, Rubella (MMR)</td>
<td>Measles IgG seronegative</td>
<td>&gt;200</td>
</tr>
<tr>
<td>Measles, Mumps, Rubella (MMR)</td>
<td>Rubella IgG seronegative women of child-bearing age</td>
<td>&gt;200</td>
</tr>
</tbody>
</table>

* Please refer to relevant chapters for the specific indications
### Table 7. Vaccines for travel-related indications*

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Recommendation</th>
<th>CD4 count (cells/mm³)</th>
</tr>
</thead>
</table>
| **Mandatory vaccines for travel to selected countries**
| Meningococcus-ACWY                           | Follow standard guidelines               | Any                   |
| Yellow fever                                 | Considered if at true risk of infection | >200                  |
| **Routine vaccines**                         |                                         |                       |
| Hepatitis A                                  | Follow standard guidelines               | Any                   |
| Hepatitis B                                  | Recommended regardless of travel         | Any                   |
| Measles, Mumps, Rubella (MMR)                | Recommended regardless of travel         | >200                  |
| Tetanus-Diphtheria/Polio myelitis-parenteral (Td/IPV) | Recommended every 10 years               | Any                   |
| **Vaccine for selective use for travellers to risk areas**
| Cholera WC/rBS                               | Follow standard guidelines               | Any                   |
| Japanese encephalitis                        | Follow standard guidelines               | Any                   |
| Tick borne encephalitis                      | Follow standard guidelines               | Any                   |
| Typhoid-ViCPs                                | Low threshold for offering vaccine       | Any                   |
| Rabies                                       | Low threshold for offering vaccine       | Any                   |

*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.

bAlthough not mandatory these vaccines are generally recommended for travellers.

Recommendations for these vaccines depend on the countries of destination, the epidemic situation at the time of travel, the purpose for travel, the intended length of stay and the health status of the traveller. Up to date health information for specific destinations is available from CDC ([http://www.cdc.gov/travel/](http://www.cdc.gov/travel/)) and WHO ([http://www.who.int/ith/en/](http://www.who.int/ith/en/)).

* Please refer to relevant chapters for the specific indications
<table>
<thead>
<tr>
<th>Disease</th>
<th>Recommendations</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax</td>
<td>Antibiotic prophylaxis ± vaccine</td>
<td>As soon as possible</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Antibiotic prophylaxis and Td/IPV vaccine</td>
<td>As soon as possible</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>If susceptible, vaccine and HNIG</td>
<td>Within 14 days and up to 28 days</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Previously unvaccinated: vaccine and HBIg</td>
<td>Within 2 days and up to 7 days</td>
</tr>
<tr>
<td></td>
<td>Previously vaccinated with HBsAb response &lt;10 IU/L: 1 booster dose + HBIg</td>
<td>May be considered up to 6 weeks</td>
</tr>
<tr>
<td></td>
<td>Previously vaccinated with HBsAb response &gt;10 IU/L: 1 booster dose; add HBIg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>if CD4 &lt;200</td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>Antibiotic prophylaxis</td>
<td>As soon as possible</td>
</tr>
<tr>
<td>Influenza</td>
<td>Consider chemoprophylaxis</td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>HNIG</td>
<td>Within 5 days</td>
</tr>
<tr>
<td>Meningococcus</td>
<td>Antibiotic prophylaxis and vaccine if in contact with group ACW or Y</td>
<td>As soon as possible</td>
</tr>
<tr>
<td>Pertussis</td>
<td>Antibiotic prophylaxis</td>
<td>Within 21 days</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>HNIG unless known to be seropositive for all 3 polio types</td>
<td>As soon as possible</td>
</tr>
<tr>
<td>Rabies</td>
<td>Vaccine ± HRIG  See Rabies chapter</td>
<td></td>
</tr>
<tr>
<td>Tetanus</td>
<td>Td vaccine ± TIG  See Tetanus chapter</td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td>CD4 &lt;400: VZIG  See Varicella chapter</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD4 &gt;400: Consider vaccine</td>
<td></td>
</tr>
</tbody>
</table>

Td/IPV: Tetanus-Diphtheria/parenteral poliovirus  
HNIG: Human Normal Immunoglobulin  
HBIg: Hepatitis B Immunoglobulin  
HRIG: Human Rabies Immunoglobulin  
TIG: Tetanus Immunoglobulin  
VZIG: Varicella-zoster Immunoglobulin

* Please refer to relevant chapters for the specific indications
Anthrax

1. Background

1.1 Bacillus anthracis
Anthrax is caused by *B. anthracis*, a toxin-producing gram positive bacterium. The infection is transmitted through spores that can be found in animal products and may remain viable in the environment for years or decades.

1.2 Clinical features
Anthrax may present as one of three main syndromes: cutaneous following direct contact (>95% of cases, rare mortality), respiratory following inhalation (50% mortality), and very rarely gastrointestinal following ingestion (mortality 25-60%). Meningitis may complicate other forms of disease 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.

1.3 Epidemiology
Disease occurs primarily in herbivorous mammals, but birds and other animals may also become infected. Human infection is rare. The disease occurs in Asia, Africa and parts of Europe and the Americas, but is uncommon in the UK [1]. There is some concern that anthrax may be used as a form of bio-terrorism [2].

1.4 Transmission
Human infection occurs almost exclusively after contact with infected animals and animals products (e.g., during industrial handling of animal hide or hair). Person-to-person transmission following contact with skin lesions may occur but is unusual. Modes of transmission include: a) Cutaneous contact with spores, spore contaminated materials or infected skin lesions; an existing break in the skin is required to initiate infection, though in many cases this may be so small as to be unnoticed; b) Inhalation of spores, and c) Ingestion of contaminated meat.

1.5 Incubation period
Usually 1-7 days, but may range from less than 1 days to 8 weeks.

1.6 Risk groups
In the UK human anthrax is rare and is almost entirely seen as an occupational disease affecting those handling imported infected animal products or working with infected animals. Cases have been reported in slaughterhouse/abattoir workers, tannery/leather workers, farm workers, butchers, engineers, textile workers and bone meal workers.

1.7 Anthrax in HIV-infected persons
It is not known whether the natural history of anthrax is modified by HIV infection.
2. Pre-exposure prophylaxis: Anthrax vaccine

2.1 Vaccine composition
The anthrax vaccine is inactivated. The active ingredient is a sterile filtrate of an alum precipitated anthrax antigen derived from the Sterne strain of *B. anthracis*. In the UK the only licensed anthrax vaccine is manufactured by the Health Protection Agency for and on behalf of the UK Government. It is 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 not produced commercially and cannot be purchased.

2.2 Route of administration
The vaccine is given by intramuscular injection (or subcutaneously in persons with bleeding disorders), preferably in the deltoid.

2.3 Schedule of administration in the general healthy population
The anthrax vaccine is not recommended for the general public and is only indicated for persons at the highest risk of occupational exposure [1]. In the event of a deliberate release, individual risk would be assessed on a case-by-case basis [1]. The primary course consists of 4 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.

2.4 Vaccine efficacy in healthy individuals
There have been no formal efficacy trials with the UK vaccine.

2.5 Vaccine efficacy in HIV-positive persons
There are no data on vaccine efficacy in HIV-infected persons.

2.6 Duration of protection
A single booster dose is given once a year.

2.7 Adverse events
The anthrax vaccine is safe [3]. Mild injection site reactions may occur. More rarely, lymphadenopathy, fever, flu-like symptoms, rash, itching or other allergic reactions may occur.

2.8 Contraindication
- A history of previous severe adverse reaction or allergy to the vaccine or its components.
- Persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated.
- The vaccine may be used in pregnancy or during breastfeeding if clinically indicated.

2.9 Pre- and post-vaccination testing
None recommended
3. Recommendations for pre-exposure prophylaxis HIV-infected adults
   - In the UK the vaccine is indicated only in those with a significant occupational risk of exposure (e.g., laboratory workers, those handling animal hides). HIV-infected adults can be offered vaccination if they belong to a group at recognised risk of exposure (C, IV). HIV-infected persons, particularly those with advanced disease, may make a suboptimal response to vaccination.

4. Post-exposure prophylaxis
   Following credible or confirmed exposure to anthrax, the person at risk should begin post-exposure prophylaxis with oral ciprofloxacin, doxycycline, or amoxicillin (if the strain is susceptible) for 60 days and may also be given the vaccine. Immunisation is recommended because of the uncertainty of when or if the inhaled spores may germinate. Advice must be obtained from the Immunisation Department of the Health Protection Agency Centre for Infections (020 8200 6868).

References

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1. Background

1.1 Vibrio Cholerae

*V. cholerae* is a non-invasive gram-negative bacterium that colonises the small bowel and secretes a toxin consisting of 5 receptor-binding B subunits and 1 active A subunit. Classification into over 100 serogroups is based on the polysaccharides of the somatic (O) antigen. Two biotypes of the O1 serotype - Classic and El Tor - are described. Man is the only known host.

1.2 Clinical Features

The disease is characterised by sudden onset of painless, profuse watery diarrhoea [1]. In its extreme form, cholera can be rapidly fatal with hypotension and death occurring within 6-8 hours of the onset of symptoms. The majority of infected people however have mild diarrhoea or may be asymptomatic. Typical, moderate to severe cholera occurs in less than 20% of infections. The disease responds to fluid- and electrolyte-replacement therapy. Aggressive rehydration is required for all but the mildest cases.

1.3 Epidemiology

Seven cholera pandemics have been recorded throughout history. The latest started in 1961 and it is still ongoing. The main affected regions are in parts of Asia, the Middle East, Africa, and Central and Latin America. The epidemics are caused by the O1 serogroup, and more recently by the O139 serogroup in South and South-East Asia [1]. There are 3-8 million cases of cholera each year and this infection continues to cause epidemics in refugee camps and in resource-poor countries where the normal infrastructure has broken down. Large outbreaks are usually caused by a contaminated water supply. In developed countries imported cases are reported sporadically in travellers to endemic countries. Cholera is rarely reported in UK travellers, predominantly among those who travel to the Indian subcontinent.

1.4 Transmission

The infection is acquired through the faecal-oral route, primarily by consuming contaminated water or food; person-to-person transmission is rare.

1.5 Incubation period

From less than 1 day to 5 days.

1.6 Risk groups

Travellers who follow usual tourist itineraries, use standard accommodations, and observe food safety recommendations while in countries reporting cholera have little risk [2]. The overall risk is two to three cases per million travellers. 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. These may include: aid workers assisting in disaster relief or refugee camps [3] and adventurous backpackers travelling to remote areas with no access to medical care. Persons with underlying
gastrointestinal disease or immunocompromise may be at increased risk for severe disease.

1.7 Cholera in HIV-infected persons
It is uncertain whether the natural history of cholera is modified by HIV infection.

2. Pre-exposure prophylaxis: Cholera vaccine

2.1 General features
The old parenteral vaccine based on inactivated phenol-killed whole-cell *V. cholerae* O1 showed modest (approximately 50%) and short-lived (<6 months) protective efficacy and did not prevent transmission. Although the vaccine is still produced in some countries, its use is not generally recommended [4]. New cholera vaccines are under development and several oral vaccines have become available internationally. These vaccines appear to provide better and more durable immunity (over 70% protection for at least one year) and have fewer adverse effects than the parenteral vaccine [5]. The oral WC/rBs vaccine is available in the UK. Production of the live attenuated CVD 103-HgR* vaccine has currently been discontinued by the manufacturers. Although this vaccine has been used in HIV-endemic areas without serious adverse events, it is contraindicated in HIV-infected persons due to insufficient safety data.

2.2 Vaccine composition
The WC/rBS vaccine contains inactivated Inaba (including El-Tor biotype) and Ogawa strains of *Vibrio cholerae*, serotype O1 together with recombinant B-subunit of the cholera toxin produced in Inaba strains of *V.cholerae*, serotype O1.

2.3 Route of administration
The WC/rBs vaccine is given orally.

2.4 Schedule of administration in the general healthy population
The vaccine is given in two doses at least 1 week (usually 10-14 days) apart [4]. Administration of two vaccine doses at 7, 14 or 28-42 day intervals results in comparable antitoxin responses in serum [6]. If more than six weeks have elapsed since the first dose, the course should be recommenced.

2.5 Vaccine efficacy in healthy individuals
The vaccine confers 85–90% protection, starting 10 days after the second dose. In a field trial in Bangladesh, three doses of the vaccine conferred 85% (95% confidence interval: 56% to 95%) protection in adults after 4–6 months, and 50% after three years [7]. In an efficacy field trial conducted in Peru, involving military personnel, two doses of the vaccine given 1-2 weeks apart provided protection in 86% of vaccine recipients followed up for a mean of 18 weeks (median 21 weeks) [8]. The WC/rBS vaccine is not expected to confer protection against *V. cholerae* O139. The vaccine appears to provide also approximately 60% protection against travellers' diarrhoea caused by heat-labile toxin-

*Contraindicated in HIV-infected persons*
producing Escherichia coli during the first 3 months following vaccination, but data are limited [4].

2.6 Vaccine efficacy in HIV-positive persons
There have been no specific reports of WC/rBS vaccine efficacy in HIV-positive individuals published to date but a recent study conducted in Beira, Mozambique demonstrated promising results in a population in which approximately 25% were HIV-positive (Per-Arne Parment, personal communication). Duration of immunity is unknown in HIV-infected persons. HIV-infected adults with CD4 counts <100 cells/mm$^3$ may be expected to respond poorly to immunization, whereas those with CD4 counts >100 cells/mm$^3$ show improved responses after two doses [9]. These observations indicate a potential benefit of vaccination in those with early and moderately advanced clinical HIV disease [8].

2.7 Duration of protection
The level of protection is approximately 50% after 3 years. A single booster dose is recommended after two years. If more than two years have elapsed since completion of the primary vaccine course, the primary course should be repeated. There is insufficient evidence to alter these recommendations in HIV-infected persons, but duration of immunity may be reduced compared with HIV-negative persons.

2.8 Adverse events
The vaccine may cause occasional gastrointestinal symptoms. Rarely, fever, malaise, nausea, vomiting, loss of appetite and dizziness have been described. Very rare adverse events included fatigue, dyspepsia, shivers, joint pain, sore throat, sweating, insomnia and rash.

The vaccine is well tolerated in HIV-infected people. Vaccination may result in a transient rise in plasma HIV load but no long term effects have been reported [10].

2.9 Contraindications
- A history of previous severe adverse reaction or allergy to the vaccine or its components.
- Persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated
- Although the safety of the vaccine in pregnant women has not been studied, the risk is considered to be minimal and vaccine use may be considered in high risk situations. The vaccine has been shown to be well tolerated in breastfeeding women.
- The vaccine should not be co-administered with other oral vaccines

2.10 Pre- and post-vaccination testing
None recommended
3. **Recommendation for pre-exposure prophylaxis in HIV-infected adults:**
   - The main indication for vaccination against cholera is protection of the population at risk in endemic areas. 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. These may include: aid workers assisting in disaster relief or refugee camps, backpackers travelling to remote areas with no access to medical care, and travellers with underlying disease or immunocompromise. Currently, no country requires proof of vaccination against cholera as a condition for entry and the International Certificate of Vaccination no longer provides a specific space for recording cholera vaccinations. Local authorities, however, may require documentation of vaccination. In such cases, the vaccine may be administered, or the traveller may be issued with a medical waiver.
   - 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).
   - Where immunization is indicated, HIV-infected persons should be given the WC/rBS vaccine in two oral doses given at least 1 week apart according to standard guidelines (see section 2.5) (C, IV). A single booster dose should be given after two years if continued protection is required, according to standard guidelines (see section 2.8) (C, IV).
   - Since the level and duration of protection may be reduced in HIV-infected persons, measures to limit risk from food and water should be emphasized.

4. **Passive immunoprophylaxis**
   Not available.

5. **Post-exposure prophylaxis**
   Not applicable

6. **Auditable outcomes**
   None

**References**


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Diphtheria

1. Background

1.1 Corynebacterium
Diphtheria is an acute infectious disease caused by toxigenic strains of the bacteria *C. diphtheriae* or *C. Ulcerans*.

1.2 Clinical features
The disease affects the upper respiratory tract and occasionally the skin. Typically symptoms include inflamed membranes of the nose and throat that can lead to total obstruction of the larynx. Life threatening complications include cardiac failure and paralysis.

1.3 Epidemiology
Prior to the introduction of vaccine diphtheria was a highly endemic disease in the UK with the average annual number of cases around 60,000 with 4,000 deaths [1]. Diphtheria vaccine was introduced in the UK in the 1940’s and mass vaccination resulted in a remarkable decline in morbidity and mortality of the disease. The vaccine became incorporated into childhood immunisation programmes throughout Europe in the 1950s and 1960s. In industrialised countries with high vaccine coverage such as the UK, the circulation of *C. diphtheriae* has virtually ceased and there is little now little possibility of acquiring natural immunity or boosting declining immunity with subclinical infection. From 1985-2004 there were 39 laboratory confirmed cases of diphtheria infection in England and Wales due to toxigenic *C. diphtheriae* and 50 laboratory confirmed infections due to *C. ulcerans* [2]. Two deaths from diphtheria have occurred in this period [3].

Circulation of toxigenic strains of *C. diphtheriae* however persist in much of the world and diphtheria cases continue to be reported from the Indian subcontinent, South East Asia, South America and Africa. The potential for infection and re-introduction into the UK through travel to and emigration from these regions therefore remains a real possibility. In addition, recent epidemics in the Russian federation have illustrated the opportunistic nature of diphtheria and how rapidly a well controlled disease could re-emerge if vaccine coverage is not maintained.

1.4 Transmission
The disease is transmitted via airborne droplets generally as a result of close contact with infectious patients or carriers. The normal reservoir of *C. ulcerans* is cattle and rarely human cases have been associated with the consumption of raw unpasturised dairy products.

1.5 Incubation period
The incubation period is from 2-5 days. Patients with untreated disease may be infectious for up to four weeks. Carriers may be asymptomatic and can transmit the infection for longer.

1.6 Risk groups
Susceptibility to diphtheria disease increases with age and currently it is estimated that approximately 50% of UK adults over age 30 years are susceptible to diphtheria. Fortunately, adults living in the UK are unlikely to come into contact with toxigenic strains of *C. diphtheriae* due to successful childhood immunisation programmes. Travel to endemic countries and close contact with cattle or other farm animals, are potential risk factors for infection.

1.7 Diphtheria in HIV-infected persons
It is uncertain whether the natural history of diphtheria is modified by HIV infection.

2. Pre-exposure prophylaxis: Diphtheria vaccine

2.1 Vaccine composition
The vaccine is made from cell-free purified toxin extracted from *C. diphtheriae*, treated with formaldehyde and converted into diphtheria toxoid. This is adsorbed on to an adjuvant, either aluminium phosphate or aluminium hydroxide, to improve immunogenicity.

2.2 Route of administration
The vaccine is administered by intramuscular injection (or subcutaneous injection in persons with bleeding disorders), preferably in the deltoid. The vaccine must not be administered via the intradermal or intravenous routes.

2.3 Schedule of administration in the general healthy population
The diphtheria vaccine is given to adults as part of a combined vaccine with tetanus and inactivated polio vaccine (Td/IPV). This preparation contains a lower dosage of diphtheria toxoid than other similar preparations designed for use in childhood [3]. A primary course consists of 3 doses of a diphtheria-containing vaccine administered at least one month apart. A booster dose should be given 5 years after primary course and a further booster 10 years later (making a total of 5 doses). There is no need to restart a series if more than the recommended time between doses has elapsed.

2.4 Vaccine efficacy in healthy individuals
The diphtheria vaccine is estimated to have clinical efficacy of over 97% [4]. Studies in HIV-negative adults have shown that protective anti-toxin level develop in 95% of previously unimmunised individuals following 3 primary doses, spaced at appropriate intervals [5]. Studies have also reported adequate anamnestic responses following a booster dose in previously immunised adults [6].

2.5 Vaccine efficacy in HIV-negative persons
Toxoid vaccines are known to be safe in HIV positive adults [7] but limited data exists on the immune response or the clinical efficacy of the vaccine in such individuals. Toxoid vaccination has been shown to provoke an immune response in HIV positive individuals; however the response may be lower compared with those uninfected [8]. Studies in children with HIV have shown that protective serological responses to diphtheria after primary series of Tetanus/Diphtheria vaccination develop in 18-76% [9]. These children show lower serum concentrations of diphtheria antitoxin compared with age-matched controls.

Adults who receive full primary vaccinations before acquiring HIV infection have been shown to have similar levels of antibody to non-infected controls, whereas the response to a booster of diphtheria toxoid is significantly reduced [8]. Patients in the earlier stages of infection are more likely to mount a protective antibody response than those with HIV related symptoms [10]. As a general rule, the lower the patients CD4 count the less likely individuals are to show vigorous response to vaccination [11]. Responses to vaccination in individuals with HIV are unpredictable and protective antibody levels may decline as immune function deteriorates [7].

2.6 Duration of protection
For most individuals a minimum of five doses of diphtheria-containing vaccine are considered adequate for protection. Boosters are recommended every 10 years for individuals who may be exposed to diphtheria in the course of their work and for certain travellers, depending on destination and nature of travel.

2.7 Adverse events
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. No increased risk of side effects or adverse reactions in individuals with HIV infection [7, 13].

2.8 Contraindications
- A history of previous severe adverse reaction or allergy to the vaccine or its components.
- Persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated.
- The vaccine should not be used in pregnancy unless there is a significant risk of infection.

2.9 Pre- and post-vaccination testing
Individuals who may be exposed to diphtheria in the course of their work (e.g., laboratory workers), should be tested three months after vaccination to confirm protective immunity.

3. Recommendation for pre-exposure prophylaxis in HIV-infected adults
**Diphtheria vaccination** is recommended in all HIV-positive persons regardless of CD4 count and should be given in accordance with standard recommendations. Adults who have not previously been immunised with diphtheria or in whom vaccination status is unknown will require a full primary course (3 doses administered at least one month apart) in order to confer adequate protection. Further boosting doses should be planned at 5 and 10 years. Adults who have received a full primary course (3 doses) as an infant and booster pre-school age (total of 4 doses) require a single booster dose (C, IV).

- It seems wise to ensure that primary vaccination is completed in the early stages of disease or when the disease is well controlled on treatment. This avoids the need to consider vaccination when an adequate immune response is less likely (B, III). For those who receive the vaccine when their CD4 count is <200 cells/mm$^3$, a booster dose should be considered after HAART-induced immunoreconstitution (C, IV).
- As for healthy individuals, persons who have received a full (5 doses) vaccine course require a booster dose at 10 yearly intervals if at risk of exposure (C, IV).

4. **Passive immunoprophylaxis**
   None recommended

5. **Post-exposure prophylaxis**
   Individuals who are close contacts of a case of diphtheria should receive antibiotic prophylaxis and vaccination as soon as possible [14]. Unimmunised individuals should receive three doses of combined tetanus, diphtheria, inactivated polio vaccine (Td/IPV). Previously immunised individuals should receive a single booster dose of combined tetanus, diphtheria, inactivated polio vaccine (Td/IPV). If a booster dose was given within the past year, no additional booster is required.

   The recommended regimen for antibiotic prophylaxis for adult close contacts is:

   - A single dose of IM benzyl penicillin (1.2M units)
   - Or 500mg erythromycin every 6 hours for seven days

   Diphtheria antitoxin is only used for the treatment of confirmed diphtheria cases.

6. **Recommendations for post-exposure prophylaxis in HIV-infected adults**
   - Diphtheria post exposure prophylaxis is recommended in all HIV-positive persons regardless of CD4 count and should be given in accordance with the standard recommendations (see section 5) (C, IV).

7. **Auditable outcomes**
   Documented completion of primary vaccination (target 75%).
References


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1. Background

1.1 Haemophilus Influenzae

*H. influenzae* is a gram-negative coccobacillus. Serious infection is usually caused by strains carrying a polysaccharide capsule. Six typeable capsular serotypes have been identified (a-f).

1.2 Clinical features

The most important manifestations of disease, meningitis and pneumonia, usually occur in children below the age of 5 years, particularly in infants. Other manifestations are epiglottitis, bacteraemia, arthritis, cellulitis, osteomyelitis and pericarditis. Meningitis carries a 4-5% risk of mortality despite antimicrobial therapy, and up to 30% risk of permanent neurological sequelae (e.g. hearing loss). In the prevaccine 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.

1.3 Epidemiology

*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 *H. influenzae* disease. In addition to direct protection of vaccinated individuals, it appears that non-vaccinated individuals have been afforded protection through the induction of herd immunity.

1.4 Transmission

*H. influenzae* is transmitted through contact with respiratory droplets.

1.5 Incubation period

Secondary *H. influenzae* disease is defined as illness occurring 1–60 days following contact with an ill child.

1.6 Risk groups

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 immunocompromise due to disease or treatment, including HIV infection

1.7 *H. influenzae* in HIV-infected persons

The risk of infection is greater in HIV-seropositive adults than in HIV-seronegative individuals. In one study the cumulative incidences of invasive *H. influenzae* disease in men 20-49 years with HIV infection or AIDS were 14.6 and 79.2 per 100,000 respectively. Only 33% of cases were due to HiB [1].
2. Pre-exposure prophylaxis: Hib vaccine

2.1 Vaccine composition
Hib vaccines are protein-polysaccharide conjugates. The protein carrier may include diphtheria toxoid, diphtheria toxoid-like protein, tetanus toxoid, or meningococcal outer membrane protein. Vaccines available in the UK are conjugated with wither CRM197 (a non-toxic variant of diphtheria toxin) or tetanus toxoid [2].

2.2 Route of administration
The Hib vaccine is given by intramuscular injection (or subcutaneous injection in persons with bleeding disorders), preferably in the deltoid.

2.3 Schedule of administration in the general healthy population
Hib vaccination is part of the UK routine childhood vaccination programme, where vaccine is given as either combined diphtheria/tetanus/acellular pertussis/inactivated polio vaccine/Hib (DTaP/IPV/Hib) vaccine, or as a single Hib vaccine [2]. One single vaccine dose is recommended in adults.

2.4 Vaccine efficacy in healthy individuals
The Hib conjugate vaccine is highly immunogenic in infants. More than 95% develop protective antibody levels after a primary series of two or three doses. Clinical efficacy has been estimated at 95% to 100%.

2.5 Vaccine efficacy in HIV-positive persons
The Hib conjugate vaccine is immunogenic in patients with HIV infection. However immunogenicity varies with stage of infection and degree of immunocompromise [3-7]. There are no data on clinical efficacy of vaccination.

2.6. Duration of protection
The duration of protection is unknown. No booster doses are currently recommended for children who have received a complete course of three injections. Vaccine-induced immunity is likely to wane with deteriorating CD4 count in HIV-infected persons.

2.7 Adverse events
Injection site reactions, including swelling, redness, or pain have been reported in 5%-30% of recipients and usually resolve within 12–24 hours. 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.

2.8 Contraindications
- A history of previous severe adverse reaction or allergy to the vaccine or its components.
- Persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated.
- The Hib vaccine may be given to pregnant women when clinically indicated.
2.9 Pre- and post-vaccination testing
Not routinely recommended.

3. Recommendation for pre-exposure prophylaxis in HIV-infected adults:
• Hib vaccination is not routinely recommended in HIV-positive adults. However, where HIV-infected adults are scheduled to receive other vaccines, a multivalent vaccine including Hib may be considered (C, IV)
• The following HIV-infected adults, whether or not immunised in infancy, should receive one Hib vaccine dose: 1) those who acquire splenic dysfunction and b) those who are contacts of a case of invasive disease (C, IV)
• HIV-infected adults who develop Hib disease and have other risk factors for further Hib disease should be offered one vaccine dose after recovery (C, IV)
• HIV-infected adults with recurrent pulmonary infections or other risk factors for severe disease should be considered for vaccination with one Hib dose (C, IV)
• Responses to the vaccine may be reduced in patients with CD4 counts <200 cells/mm\(^3\). If vaccination is indicated in a HIV-infected person, re-immunisation should be considered after HAART-induced immunoreconstitution (C, IV).

4. Passive immunoprophylaxis
None recommended

5. Post-exposure prophylaxis
Where there is a HIV-infected individual in the household of a Hib case, the index case and all household contacts should be given rifampicin prophylaxis, regardless of their immunisation status. The recommended dose is 20 mg/kg/day (up to a maximum of 600 mg daily) once daily for four days. Patients on HAART may take ciprofloxacin as an alternative to rifampicin.

6. Auditable outcomes
HIV-infected persons who acquire splenic dysfunction should receive one Hib vaccine dose (Target 95%)
HIV-infected contacts of a case of invasive disease should be offered one vaccine dose (Target 75%)

References


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1. Background

1.1 Hepatitis A virus
The Hepatitis A virus (HAV) is a Picornavirus. A single serotype exists worldwide.

1.2 Clinical features
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. Hospitalisation is required in approximately one fifth of symptomatic cases. Fulminant hepatitis occurs rarely (<1% overall) but carries a greater than 50% risk of mortality. Although approximately 15% of infected persons show prolonged or relapsing symptoms over a 6 to 9 month period, chronic infection is not known to occur. Infection is followed by life-long immunity.

1.3 Epidemiology
HAV prevalence is high to intermediate in Central and South America, the Caribbean, Mexico, Africa, Asia (except Japan), and Eastern Europe.

1.4 Transmission
HAV is 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 [1-5].

1.5 Incubation period
28 days (range 15-50 days).

1.6 Risk groups
Those at risk for HAV infection include the following:
- Household contacts of infected persons
- Sexual contacts of infected persons
- Persons travelling to countries where hepatitis A is common (excluded Australia, New Zealand, Japan, North America, northern and Western Europe)
- Men who have sex with men
- Injecting and non-injecting drug users
- Individuals at risk 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

Those at risk for complications include the following:
- Patients with chronic liver disease and chronic infection with hepatitis B or hepatitis C are at risk for severe disease and acute liver failure [6, 7]
1.7 *Hepatitis A in HIV-infected persons*
Hepatitis A does not appear to be worse in HIV-infected patients when compared with HIV-negative persons [8], although HAV viraemia may be prolonged [9].

2. Pre-exposure prophylaxis: Hepatitis A vaccine

2.1 Vaccine composition
The vaccine is prepared with formaldehyde-inactivated HAV grown in human diploid cells. There are also combined hepatitis A/hepatitis B and hepatitis A/typhoid vaccines.

2.2 Route of administration
The HAV vaccine is given by intramuscular (or deep subcutaneous injection in case of bleeding disorders), preferably in the deltoid.

2.3 Schedule of administration in the general population
The HAV vaccine is given in two doses at 0 and 6-12 months. The combined hepatitis A/hepatitis B vaccine is usually given at 0, 1 and 6 months.

2.4 Vaccine efficacy in healthy individuals
The hepatitis A vaccine is highly immunogenic and efficacious. Protective levels of antibodies develop in 97-100% of healthy individuals within one 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 HAV and HBV vaccine is also highly efficacious [10].

2.5 Vaccine efficacy in HIV-positive persons
Response rates to HAV vaccination are reduced in HIV-infected persons and HAV antibody levels may be lower and decline more rapidly compared with HIV-negative persons. Responses correlate with the CD4 count at the time of vaccination [11-16], but not with the nadir CD4 count [15]. Seroconversion rates are 50-95% overall [16], but can be as low as 9% in people with CD4 count <200 cells/mm$^3$ [13]. Responses are 95-100% in persons with CD4 count >300-500 cells/mm$^3$. Undetectable plasma HIV RNA on HAART is associated with higher anti-HAV antibody levels [13]. Increasing the number of doses may improve responses.

2.6 Duration of protection
Successful immunisation in healthy persons is thought to confer protection for over ten years; current opinion suggests that immunity may be lifelong. Duration of protection in HIV-infected people is unknown, but may be shorter than in HIV-negative persons.

2.7 Adverse events
The HAV vaccine is safe and well tolerated in HIV-infected individuals [12, 13]. 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.
2.8 Contraindications
- A history of previous severe adverse reaction or allergy to the vaccine or its components.
- Persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated.
- There is no evidence that the vaccine causes damage to the foetus. However, it should not be given during pregnancy unless there is a specific indication. Because the vaccine is produced from inactivated HAV, the theoretical risk to the developing foetus is expected to be low.

2.9 Pre- and post-vaccination testing
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, homosexual males, injecting drug users and persons above the age of 50 years.

Routine post-vaccination testing is not generally recommended, but may be considered in selected high-risk individuals.

3. Pre-exposure prophylaxis: Human Normal Immunoglobulin
Human Normal Immunoglobulin (HNIG) in the past has been 80-90% effective in preventing clinical hepatitis for 3-6 months. In previous indications, HNIG was used together with vaccination for the pre-exposure prophylaxis of travellers, to provide immediate protection when the planned departure was less than 2-4 weeks later. However, current HNIG preparations vary in the levels of HAV antibodies and commercial supplies can no longer be relied upon to provide protection. Although effective preparations are available through the Health Protection Agency, there is not enough to supply for routine use in pre-exposure prophylaxis and supplies are only available for limited indications.

Where available, HNIG is given at the dose of 500 mg by intramuscular injection. 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. Although co-administration of HNIG and HAV vaccine has a blunting effect on the vaccine-induced antibody response, this does not appear to be clinically significant. Where indicated, HNIG and HAV vaccine can be given concurrently, using different sites.

4. Recommendation for pre-exposure prophylaxis in HIV-infected adults
- Vaccination against hepatitis A is recommended in all HIV-positive persons if they belong to a group at risk for the infection or its complications (see section 1.6) (C, IV).
• HIV-infected persons with CD4 >300 cells/mm$^3$ may follow the standard vaccination schedule (see section 2.3) (B, IIa).
• Increased number of immunisations (3 doses over 6-12 months) may increase levels and persistence of antibodies and should be given to at-risk HIV-infected persons with CD4 count <300 cells/mm$^3$ [13] (B, IIa).
• In vaccine recipients with CD4 <300 cells/mm$^3$, revaccination should be considered once the CD4 count has risen >500 cells/mm$^3$ and the viral load has become undetectable with HAART (C, IV).
• HIV-infected persons at risk for the infection should receive a boosting dose every 5 years (C, IV).
• HAV vaccine is recommended for the pre-exposure prophylaxis of HIV-infected travellers to areas of high or intermediate endemicity of hepatitis A. It needs to be given as soon as possible and at least 2 weeks before travel (C, IV). In people at very high risk of hepatitis A and its complications who are severely immunocompromised (CD4 <200 cells/mm$^3$) passive prophylaxis with HNIG may be considered together with the vaccine, after discussion with the Health Protection Agency. (C, IV)

5. Post-exposure prophylaxis
Post-exposure prophylaxis of susceptible persons with HAV vaccine and HNIG 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. HNIG preparations vary in the levels of HAV antibodies. Limited supplies are available through the Health Protection Agency for specific indications or can be bought from the Scottish National Blood Transfusion Service.

6. Recommendations for 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 is recommended in all HAV seronegative HIV-infected persons (C, IV). Administration should be given as soon as possible and should not be delayed by waiting for the hepatitis A serostatus.
• HAV vaccine and HNIG should be given together (at a different site), within 14 days of exposure. Prophylaxis may still be considered after day 14 and up to day 28 (C, IV).

7. Auditable outcomes
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%)
Complete the vaccination course within 12 months (target 90%)

References


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- **Conflict of interest:** None
1. **Background**

1.1 **Hepatitis B virus**  
The hepatitis B virus (HBV) is a member of the hepadnaviridae family. There are four serotypes (adw, ayw adr, ayr) and eight genotypes (A-H); their distribution varies geographically.

1.2 **Clinical features**  
The severity of acute hepatitis B varies from asymptomatic infections 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 HBV infection can lead to chronic liver disease, cirrhosis and hepatocellular carcinoma.

1.3 **Epidemiology**  
The World Health Organization estimates that more than 350 million people are chronically infected with HBV worldwide, and that 1 million deaths occur annually as a result of the infection. Based on the prevalence of the infection, three 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 [1].

1.4 **Transmission**  
HBV is transmitted through sexual intercourse, percutaneous and parenteral exposure to blood and infected body fluids, and vertically from mother to child.

1.5 **Incubation period**  
90 days (range 40-160 days).

1.6 **Risk groups**  
The risk of exposure to HBV infection is increased in intravenous 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 handicap, and travellers to areas of high prevalence. The risk of chronicity after infection is increased in those with immunodeficiency due to disease or treatment.

1.7 **Hepatitis B in HIV-infected persons**  
Chronic HBV infection is found in 6-10% of HIV-infected persons in the UK [2, 3]. The risk factors for HBV infection are similar to those for HIV infection, which in part explains the high prevalence of co-infection. This is also explained by the higher rate of development of chronic carriage in HIV-positive individuals exposed to HBV infection,
compared with HIV-negative people [4]. HIV/HBV co-infected persons show increased frequency of markers of HBV replication, with higher HBV DNA levels and lower rates of spontaneous e-antigen clearance. HIV-infected persons also show higher reactivation rates of a quiescent or resolved HBV infection, and the risk is associated with the CD4 count. In persons with chronic HBV infection, the risk of progression to cirrhosis and liver cancer is increased when there is HIV co-infection, with a 25-30% lifetime risk for either complication [2, 5]. The mortality rate of dual HIV/HBV infected patients is approximately ten times higher than of those infected with either infection alone [2, 5].

2. Pre-exposure prophylaxis: Hepatitis B vaccine

2.1 Vaccine composition
The vaccine is prepared with biosynthetic surface antigen made using recombinant technology. There is also a combined hepatitis A and B vaccine.

2.2 Route of administration
The vaccine is given by intramuscular (or deep subcutaneous injection in case of bleeding disorders), preferably in the deltoid. The buttock must never be used as it may cause reduced vaccine efficacy. Intradermal vaccination results in reduced responses rates and is not generally recommended in HIV-infected persons (C, IV).

2.3 Schedule of administration in the general population
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 [6, 7]. 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 [8]. There is limited evidence on the efficacy of the ultra-rapid schedule in HIV-infected persons. A small study showed the early antibody response to be at least equivalent to other schedules in patients with CD4 above and below 350 cells/mm$^3$ [9]. The combined A + B vaccine is usually given at 0, 1, and 6 months.

2.4 Vaccine efficacy in healthy individuals
Approximately 80-90% of young adults respond to a course of vaccine in terms of achieving serum surface antibody (HBsAb) levels >10 IU/L. An antibody level >100 IU/L is regarded as ideal whereas a level <10 IU/L is classified as non-response [10, 11]. The combined HAV and HBV vaccine is also highly efficacious [8]. Factors that reduce responses include age above 40 years, weight, female gender, haemodialysis, and smoking. Patients who are immunodeficient or on immunosuppressive therapy may respond less well than healthy individuals and may require larger doses of vaccine or additional doses [12, 13].

2.5 Vaccine efficacy in HIV-positive persons
Response rates and HBsAb levels and durability are reduced in HIV-positive people. Response rates range between 7-88% and correlate strongly with CD4 count, CD4 nadir,
and HIV-1 plasma viral load [6, 7, 14-22]. Elevated levels of CD8+/CD38+/HLA-DR+ T-cells predict reduced responses, suggesting that ongoing viral replication and concomitant immune system activation associated with HIV infection decrease the ability of the immune system to respond to vaccination [18]. Response rates are also reduced in homosexual males compared with heterosexual persons [22]. Nonetheless, HBV vaccination significantly reduces the risk of incident HBV infection in HIV-infected persons [23]. Although HBV infection can occur in HIV-infected patients who respond to vaccination, it is usually characterised by a mild course and reduced risk of chronicity.

Patients on HAART generally show improved responses [21]. Rates of achieving HBsAb levels >10 IU/L after standard vaccination are 56-88% at CD4 count >500 cells/mm$^3$, but only 25% or less with CD4 counts <350-200 cells/mm$^3$. Strategies to improve responses include revaccination of non-responders once the CD4 count is >500 cells/mm$^3$ and the plasma HIV RNA is suppressed, and the use of higher or more frequent HBV vaccine doses [7, 22, 24]. In patients with CD4 <500 cells/mm$^3$, 6 vaccine doses given at 0, 1, 2, 3, 4, 5 months induce HBsAb >10 IU/L in 92% of vaccine recipients [7]. In patients with CD4 ≥350, double-dose vaccination at 0, 1, and 6 months induces HBsAb >10 IU/L in 64% of vaccinees compared with 39% of those receiving the standard dose [22]. Of note, the improved seroconversion rate associated with the use of double-dose vaccination has not been seen in patients with CD4 <350 cells/mm$^3$ [22].

### 2.6 Duration of protection

The duration of antibody persistence is not known precisely. Successful immunisation in healthy adults prevents disease for over ten years and current opinion suggests that immunity may be lifelong [25]. 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 sub-clinical [26, 27]. There is currently lack of consensus on the requirement for booster doses of the vaccine 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. Boosting requirements are not well defined for immunocompromised patients. 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.

### 2.7 Adverse events

HBV vaccine is safe and well tolerated in HIV-infected individuals. 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. 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 [28]. It has been proposed that HBV vaccination may temporarily impair the immune response to HBV infection in HIV-1-infected persons, thus increasing the risk of chronicity should
infection occur in the few days immediately after vaccination [29]. The clinical implications of these observations are unclear, but they should not deter from offering vaccination to HIV-infected persons. Although HIV-1 plasma viral load may increase after vaccination, this is usually transient and bears no clinical significance, particularly in the context of HAART [7]

2.8 Contraindications
- A history of previous severe adverse reaction or allergy to the vaccine or its components.
- Persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated.
- There is no evidence that the vaccine causes damage to the foetus. Immunization should not be withheld from a pregnant woman if she is in a high-risk category.

2.9 Pre- and post-vaccination testing
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. No vaccination is required in these cases. The management of persons who are HBsAg negative, HBcAb positive and HBsAb negative is controversial [30]. These patients may belong to one of the following groups:
- Recent resolving HBV infection: HBV core IgM positive
- Occult HBV infection: HBV DNA positive
- Resolved HBV infection: strong HBcAb reactivity; e-antibody (HBeAb) may be positive; an anamnestic response (HBsAb >10 IU/L) is observed 1-2 weeks after a single vaccine dose [30]
- False positive HBcAb result and susceptibility to infection

Testing for HBsAb is recommended 6-8 weeks after the final vaccine dose (C, IV).

3. Recommendation for pre-exposure prophylaxis in HIV-infected adults
- Vaccination against HBV is recommended in all non-immune HIV-positive persons (B, IIb).
- HBV vaccination rates are closely dependent on the clinical setting providing HIV care [21], indicating that compliance should be audited regularly.
- Trials are under way to determine whether the ultra-rapid vaccination schedule is effective in HIV-infected persons. Based on available evidence, only the standard and rapid schedules can be recommended (C, IV). However, the ultra-rapid schedule may be considered in selected patients with good immune status (C, IV).
- The HBsAb level should be measured ideally 6-8 weeks after vaccination. Vaccine recipients with HBsAb <10 IU/L should be offered three additional doses, which can be administered at monthly intervals [7] (B, IIa). The use of double-dose vaccine should be considered if the CD4 count is ≥350 (B, IIa), but there is no evidence currently to support its use at lower CD4 counts. Depending on the level of risk, re-
vaccination may be delayed until the CD4 count has risen >500 cells/mm³ on HAART (B, IIa). Vaccine recipients with a response >10 but <100 IU/L should be offered one additional vaccine dose (C, IV).

- Following successful immunisation, the HBsAb level should be measured yearly. A booster should be offered to persons with HBsAb level <100 IU/L (C, IV).
- HBV vaccination should be considered in patients who are HBsAg negative, HBcAb positive, HBsAb negative (see section 2.9) (B, IIa).

4. Post-exposure prophylaxis: Hepatitis B Immunoglobulin
Hepatitis B-specific immunoglobulin (HB Ig) can protect from infection or attenuate disease if given immediately before or soon after exposure to HBV. HB Ig is not generally recommended for pre-exposure prophylaxis due to high cost and short-lived efficacy [1] (C, IV). HB Ig is recommended for the post-exposure prophylaxis of susceptible persons following a significant exposure to infection, when it is usually combined with the HBV vaccine [31]. Among HIV-negative people, only 1% develop disease and 2% have evidence of infection if prophylaxis is given within 7 days of exposure [32]. In addition, a rapid vaccination course started within 7 days of exposure appears to be as effective as vaccination plus HB Ig [31]. There are no data on the efficacy of post-exposure prophylaxis in HIV-infected persons.

HB Ig is available from the Health Protection Agency.

4.1 Route of administration
HB Ig (500 units) is given by intramuscular injection. When given with the HBV vaccine, a different injection site should be used.

4.2 Schedule of administration
Post-exposure prophylaxis should be given within 2 days and up to 7 days after exposure [32]. For sexual partners of persons with acute hepatitis B, prophylaxis should be started preferably within 7 days of the onset of jaundice in the index case. Efficacy of post-exposure prophylaxis beyond 7 days is unknown [20, 21], but may be considered up to 6 weeks after exposure; specialist advice should be sought.

Two doses of HB Ig are recommended, given one month apart.

4.3 Duration of protection
HB Ig affords protection for 3-6 months [1].

4.4 Adverse events
Minor local reactions can occur at the injection site. Rarely anaphylaxis has been observed.
### 4.5 Pre-immunisation testing

Following a high risk contact, screening for HBV markers should be considered if the information is not already available. Testing should not delay the start of post-exposure prophylaxis.

### 5. Recommendations for post-exposure prophylaxis in HIV-infected adults

- Following a high-risk exposure, the HBV immune status should be determined if unknown.
- No prophylaxis is required in those with evidence of a past HBV infection (HBsAg negative, HBCab positive, HBsAb positive) (C, IV).
- 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 <200 cells/mm$^3$) since the recorded response to vaccination, HB Ig should also be given (C, IV).
- Non-responders (HBsAb <10 IU/L) to previous vaccination should be offered a booster dose of the vaccine and HB Ig (C, IV).
- Those who have not been previously vaccinated should be offered a rapid course of vaccination and HB Ig (C, IV).
- Patients requiring HB Ig should receive two doses, one 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. Post-exposure prophylaxis beyond 7 days and up to 6 weeks after exposure may be considered; specialist advice should be sought (C, IV).

### 6. Auditable outcomes

Test newly diagnosed HIV-infected patients for hepatitis B infection and immunity within 3 months of HIV diagnosis (target 95%)

Offer hepatitis B vaccination to HIV-infected patients who are non-immune within 6 months of HIV diagnosis (target 95%)

Complete vaccination course (target 95%)

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

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1. **Background**

1.1 **Influenza viruses**

There are three types of influenza viruses – A, B and C. Influenza A and influenza B account for most cases of disease. Influenza A viruses are antigenically variable due to 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 subtypes which, 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.

1.2 **Clinical features**

Influenza is characterized by the abrupt onset of constitutional and respiratory symptoms, including fever, malaise, myalgia and dry cough. Severity varies from asymptomatic or minimally symptomatic to severe and even fatal infections. Influenza is usually self-limiting and resolves within 2-7 days in uncomplicated cases. It 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 cardio-pulmonary causes, mainly among the elderly. Rarely, influenza has been associated with encephalopathy, transverse myelitis, myositis, myocarditis, pericarditis and Reye’s syndrome. Although effective antiviral treatment is available, vaccination remains the most effective measure to limit the impact of influenza.

1.3 **Epidemiology**

Outbreaks of infection with influenza A occur most years and these are the usual cause of epidemics. Influenza B infection can also cause outbreaks, usually between outbreaks of influenza A; they tend to be less extensive and to be associated with less severe illness. In the tropics influenza occurs all year round. The influenza season is October through May in the Northern hemisphere and April through September in the Southern hemisphere.

1.4 **Transmission**

Influenza is highly infectious. Transmission occurs through the respiratory tract via both large droplets and small aerosolised particles.

1.5 **Incubation period**

2-3 days (range 1-7 days).

1.6 **Risk groups**

Influenza affects all age groups, but the greatest morbidity and risk for complications, hospitalization and deaths 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 immunocompromise.

1.7 Influenza in HIV-infected persons
There is limited information concerning the impact of influenza on morbidity and mortality in HIV-infected adults. Available evidence suggest an increased risk of complications, impairment of respiratory function with hypoxaemia, prolonged duration of illness and increased rates of hospitalisation secondary to influenza-related morbidity [1-4]. Data from the pre-HAART era indicated that patients with AIDS had substantial excess mortality due to pneumonia or influenza during influenza seasons, with rates that were significantly higher than those observed in the general population and comparable or even higher than those observed in elderly persons ≥65 years [5]. It is currently unknown whether the magnitude of risk has been reduced by the introduction of HAART.

2. Pre-exposure prophylaxis: Influenza vaccine

2.1 Vaccine composition
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. Current vaccines are trivalent containing two type A and one type B sub-types. 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. A live attenuated influenza vaccine (LAIV) for intranasal administration has been approved in the United States for use in healthy people 5 years to 49 years of age.

2.2 Route of administration
The vaccine is given by intramuscular (or deep subcutaneous injection in case of bleeding disorders), preferably in the deltoid.

2.3 Schedule of administration in the general population
The influenza 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 to those who receive this vaccination later in the influenza season (until March).

2.4 Vaccine efficacy in healthy individuals
In healthy individuals vaccination gives 70-80% protection against infection with influenza virus strains related to those in the vaccine. Although responses to vaccination are often reduced in the elderly and those with underlying conditions, vaccination can still protect against severe disease and complications including bronchopneumonia, hospital admissions and mortality.
2.5 Vaccine efficacy in HIV-positive persons
Vaccine induced antibody responses are lower in HIV-infected persons compared with HIV-negative controls, especially among those with CD4 counts <200 cells/mm$^3$ [6-18]. Influenza-specific humoral and cellular immune 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/mm$^3$ while on HAART appear to have humoral and cellular responses to influenza vaccination similar to those of healthy controls [19].

Data on the clinical efficacy of influenza vaccination in HIV-infected adults are limited. Even with suboptimal antibody responses, vaccination may still protect against severe disease. In patients receiving antiretroviral therapy with a CD4 count >200 cells/mm$^3$ the estimated efficacy of vaccination against laboratory-confirmed infection ranges between 69% and 100% [20]. Protection against respiratory disease ranges between 73% and 100%. Although the protective effect is significantly reduced in patients with CD4 counts <200 cells/mm$^3$, the risk of severe disease appears to be reduced compared with unvaccinated persons [20].

2.6 Duration of protection
Development of protective antibodies occurs about 2 weeks after vaccination. Protection lasts for about one year and the vaccine is to be repeated annually

2.7 Adverse events
Influenza vaccine is safe and well tolerated in HIV-infected individuals [21]. Injection site reactions are the most frequent side effects. Rare side effects include:

- Fever, malaise, myalgia and/or arthralgia beginning 6 to 12 hours after immunisation and lasting up to 48 hours
- Allergic reactions, most likely due to hypersensitivity to residual egg protein
- Guillain-Barré syndrome has been reported very rarely after immunisation with influenza vaccine, and a causal relationship has not been established

There have been concerns that the immune activation induced by influenza vaccination may stimulate HIV replication. The evidence is controversial, with some studies showing increases in plasma or cellular HIV levels and others showing no effect [9, 11-14, 16-18, 20, 22-26]. Taken together, the available data indicate that a minority of patients experience transient and limited elevations in plasma viral load that peak at 1-4 weeks post-immunisation. The risk of viral load increases may be higher for patients not receiving HAART. These elevations do not have adverse clinical consequences in either the short or the long term [9, 11, 23, 25].

2.8 Contraindication
- Severe allergy to eggs
- A history of previous severe adverse reaction or allergy to the vaccine or its components.
- Previous Guillain-Barré syndrome within 6 weeks of receiving an influenza vaccine
• Persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated.
• There is no evidence that the inactivated influenza vaccine causes damage to the foetus. However, it should not be given during pregnancy unless there is a specific indication. With the vaccine produced from inactivated virus the theoretical risk to the developing foetus is expected to be low.
• The intranasal live attenuated influenza vaccine 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).

2.9 Pre- and post-vaccination testing
None indicated

3. Recommendation for 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, including any of the following (A Ib):
  a) Chronic respiratory disease, including asthma
  b) Significant cardiovascular disease (excluding hypertension only)
  c) Chronic renal disease
  d) Chronic liver disease
  e) Diabetes mellitus
  f) Additional immunosuppression due to disease or treatment, including asplenia or splenic dysfunction, chemotherapy, and use of oral steroids for more than a months at a dose equivalent to prednisolone 20mg or more per day, or high-dose long-acting inhaled steroids
  g) Aged ≥65 years
  h) Living in nursing homes, residential homes and other long stay facilities

• Although responses to vaccination are impaired in patients with CD4 counts <200 cells/mm³, these patients should be offered vaccination with the aim of attenuating the impact of influenza (C, IV).
• Manufacture of influenza vaccine is complex and 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 immunisation season (C, IV).

4. Antiviral therapy for pre- and post-exposure prophylaxis
Antiviral therapy with either oseltamivir (75mg orally once daily) or zanamivir (10mg 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. Please refer to BNF
or [http://emc.medicines.org.uk](http://emc.medicines.org.uk) for cautions and contraindications on the use of oseltamivir and zanamivir.

5. Recommendations for 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 <200 cells/mm$^3$ 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.
- Should a pandemic of influenza occur directives will be issued concerning the use of chemoprophylaxis in HIV-infected persons
- Post-exposure chemoprophylaxis with either oseltamivir or zanamivir started within 48 hours of a high-risk contact and given for 7 days should be considered in the following groups:
  a) Unvaccinated HIV-infected persons (C, IV)
  b) Vaccinated HIV-infected persons in whom the vaccine is not expected to be effective (CD4 count <200 cells/mm$^3$ or poor match between vaccine and circulating influenza strain) (C, IV)
  c) HIV-infected 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 <200 cell/mm$^3$ or additional risk factors (C, IV).

6. Auditable outcomes

Offer annual influenza vaccination to all HIV-infected persons. Target 95%

References


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Japanese encephalitis

1. Background

1.1 Japanese encephalitis virus
Japanese encephalitis is mosquito-borne encephalitis caused by the Japanese encephalitis virus (JEV), a member of the flaviviridae.

1.2 Clinical features
Illness ranges from asymptomatic infection to severe encephalitis with a high risk of mortality. Approximately one in every 200 infections is estimated to 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.

1.3 Epidemiology
JEV is the leading cause of viral encephalitis in Asia. The endemic zone stretches from the Indian subcontinent eastwards across Asia and Southeast 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 coexist. 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.

1.4 Transmission
The infection is transmitted to humans by the bite of *Culex* mosquitoes. Person-to-person transmission has not been reported.

1.5 Incubation period
5-15 days.

1.6 Risk groups
Travellers to rural areas of South East Asia and the Far East are considered at risk. The disease risk is extremely low, although variable according to the season, locations and duration of travel, and activities of the person. The estimated risk during a 1-month period during the transmission season is 1 per 5,000 to 1 per 20,000 per week. The overall risk for most short-term travellers may be 1 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 risk further.

1.7 Japanese encephalitis in HIV-infected persons
There are no published data indicating whether the risk of infection and disease is modified by HIV infection.
2. Pre-exposure prophylaxis: JEV Vaccine

2.1 Vaccine composition
There are two (unlicensed) vaccines available for use in the UK, both containing formalin-inactivated Nakayama strain derived from mouse brains. The vaccine must be given on a named patient basis.

2.2 Route of administration
The vaccine is given by deep subcutaneous injection.

2.3 Schedule of administration in the general healthy population
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. One additional dose is recommended a month after the initial course for those over 60 years of age. 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 due to reduced immunogenicity compared with the standard course [1].

2.4 Vaccine efficacy in healthy individuals
Three doses provide protective and sustained levels of neutralizing antibody in virtually 100% of vaccinees.

2.5 Vaccine efficacy in HIV-positive persons
No studies have been published on antibody responses to JEV vaccination in HIV-positive adults. One study in children showed a reduced response rate and lower antibody levels after two doses [2]. There no data on the immunogenicity of three vaccine doses or on the impact of HAART on vaccine responses. It should be assumed that patients with CD4 count <400 cell/mm$^3$ and especially those with CD4 count <200 cell/mm$^3$ are likely to have reduced response rates and less durable antibody responses.

2.6 Duration of protection
The duration of protection is not known. Neutralising antibody persists for at least two years after a three-dose primary course. In healthy persons, a booster is recommended after three years for those at continuing risk. There is insufficient evidence for modifying the boosting requirements in HIV-infected persons [3, 4].

2.7 Adverse events
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 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 to 104 per 10,000. Hypersensitivity reactions usually occur within 24-48 hours of immunisation but can be
delayed for 7 days after immunisation. Vaccinated persons should be monitored for 30 minutes 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 [1, 2].

2.8 Contraindication
- A history of previous severe adverse reaction or allergy to the vaccine or its components.
- Persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated.
- Anecdotal reports suggest that JE vaccine should not be used in individuals who have recovered from acute disseminated encephalomyelitis or Guillan-Barre or who have multiple sclerosis or other demyelinating disorders.
- Persons with allergic conditions should be advised about the risk of vaccine-related angioedema and generalised urticaria. A risk assessment needs to take into account the likelihood of exposure and the possible adverse effects of the vaccine.
- There is no evidence that the vaccine causes damage to the foetus. However, it should not be given during pregnancy unless there is a specific indication. A risk assessment should be made of the theoretical risks of the JEV vaccine in pregnancy against the potential risk of acquiring the infection.

2.9 Pre- and post-vaccination testing
None recommended

3. Recommendation for pre-exposure prophylaxis in HIV-infected adults
- The decision to use the JEV vaccine should balance the risks for exposure to the virus and for developing illness, the availability and acceptability of protective measures, and the side effects of vaccination. The vaccine should be considered for HIV-infected 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, vaccine should be considered for HIV-infected travellers spending <30 days in endemic areas, e.g., travellers to areas experiencing epidemic transmission and persons whose activities, such as extensive outdoor activities in rural areas, place them at high risk for exposure (C, IV).
- The vaccine is also recommended for HIV-infected expatriates whose principal area of residence is an area where JEV is endemic or epidemic (C, IV).
- HIV-infected persons should receive the standard vaccination schedule (see section 2.3). The abbreviate schedule is not recommended (C, IV).
- A booster is recommended after three years for those at continuing risk (C, IV).
- Due to the possibility of reduced responses to vaccination in HIV-infected persons, the importance of precautions against mosquito bites should be emphasised.
4. **Post-exposure prophylaxis**
None available

5. **Auditable outcomes**
Proportion of at risk HIV-infected patients who complete a 3-dose vaccination course before travelling (target 70%)

References


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Measles, Mumps and Rubella

1. Background

1.1 Measles, Mumps and Rubella viruses
Measles virus and Mumps virus are Paramyxoviruses, whereas Rubella is a Togavirus.

1.2 Clinical Features
Measles begins with a prodromal fever, conjunctivitis, coryza, cough, and Koplik spots on the buccal mucosa. A characteristic red, blotchy maculopapular rash appears around the third day of illness, beginning on the face, becoming generalized, and lasting for 5-6 days. The disease can be severe. Complications include diarrhoea (8%), otitis media (7%), pneumonia (6%), and encephalitis (0.1%), leading to death in approximately 2 of every 1,000 cases in developed countries.

Mumps begins with a prodromal fever, headache, malaise, myalgia, and anorexia, typically followed by parotitis. Up to 20% of infections are asymptomatic. Neurological complications can occur in up to 15% of clinically symptomatic cases, usually manifest as mild aseptic meningitis. Rarely, central nervous system complications can result in permanent sequelae, including deafness (1 in 20,000 cases). Orchitis may occur in 20-50% of postpubertal males. Pancreatitis occurs in 2-5% of cases. The mortality rate is between 1 and 3 per 10,000 cases.

Rubella is a mild illness characterised by low grade fever, a maculopapular rash lasting 3 days and generalized lymphadenopathy. In up to 70% of adult women it is complicated by arthralgia or arthritis. If contracted 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.

1.3 Epidemiology
Measles, mumps and rubella remain common diseases in many countries of the world. Patients are at risk while travelling abroad [1], but may also be exposed to infection in the UK [2,3]. Insufficient uptake of MMR vaccine in the UK in recent years has led to localised measles and mumps outbreaks, and endemic measles could reappear [4].

1.4 Incubation period
Measles: 10-12 days
Mumps: 14-18 days
Rubella: 12-23 days

1.5 Transmission
Measles, mumps and rubella are all transmitted by the respiratory route. Measles is highly communicable.
1.6 Risk Groups
Immunocompromised patients are at risk of severe disease and complications following infection with measles. Pregnant women are at risk of miscarriage after measles and at risk of foetal damage after rubella infection.

1.7 Measles, mumps and rubella in HIV-infected persons
There is no evidence to suggest that mumps or rubella infections are more severe in the HIV setting. Measles, however, is potentially life-threatening infection in HIV-infected adults and children. There may be no rash and the complications of measles – pneumonitis and encephalitis – may only present several months after the initial infection [5,6].

Limited data on the seroprevalence of measles IgG among HIV-infected adults indicates higher rates in those born in the pre-vaccination era than in those born later [7]. Compared with prior immunisation, natural measles prior to HIV infection affords higher and more durable serological responses and greater protection from measles. Neither a history of measles or immunisation is a reliable predictor of seropositive status [7], nor does seropositivity guarantee immunity to natural infection [8]. High-titre high-avidity rubella IgG is initially maintained following HIV seroconversion but patients with AIDS show significantly lower titres [9].

2. Pre-exposure prophylaxis: MMR vaccine

2.1 Vaccine composition
The MMR vaccine contains live attenuated viruses. The combined MMR vaccine is recommended whenever one or more of the individual components are indicated.

2.2 Route of administration
The MMR vaccine is given by deep subcutaneous or intramuscular injection preferably in the deltoid.

2.3 Schedule of administration in the general healthy population
The vaccination course consists of two doses. In children the first dose is given at 12-15 months and the second dose at 4-5 years of age. In adults, two doses should be administered to confer protection against measles, with the second dose given at any time but at least one month after the first. One vaccine dose is required to confer protection against rubella. MMR may be administered simultaneously (but in a different site) with any other live or inactivated vaccine. If other live vaccines are not given simultaneously, they should be separated by an interval of at least 4 weeks. 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.
2.4 Vaccine efficacy in healthy individuals
MMR is efficacious in the immunocompetent host [10]. Susceptibility to measles is reduced to 10% following one dose of MMR, and to 1% after completing the recommended schedule. Two vaccine doses induce sustained antibody titres to mumps and rubella in at least 95% healthy recipients [10].

2.5 Vaccine efficacy in HIV-infected persons
Limited published data show that a minority of measles IgG seronegative HIV-infected adults seroconvert following vaccination [11, 12]. Seroconversion rates for rubella are also diminished in these patients. Immune reconstitution is likely to improve seroconversion rates. Children on HAART show improved serological responses to measles following a second dose of MMR [13].

2.6 Duration of protection
In healthy individual protection is expected to be lifelong.

2.7 Adverse events
Fever and rash occur in 5-15% of vaccine recipients, usually 7-12 days after vaccination, lasting 1-2 days. These symptoms are usually attributable to the measles component. Arthralgia, arthritis or both are reported in up to 25% of vaccinated women and are usually mild and transient. Transient lymphadenopathy sometimes occurs and is attributable to the rubella component. Parotitis and deafness occurs rarely and are attributable to the mumps component. Allergic reactions have been reported, but severe anaphylaxis is estimated to occur less than once per million doses. Clinically apparent thrombocytopenia has been observed (<1 in 30,000 doses). Neurological complications, including aseptic meningitis, encephalitis, and encephalopathy, have been reported, but are very uncommon (<1 in one million 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.

In general MMR vaccination is safe in HIV-infected adults and prior to 1993 was advocated for asymptomatic and symptomatic patients [14]. The change in policy was prompted by a case of fatal measles vaccine-associated pneumonitis in a 20 year old severely immunocompromised HIV-infected male, presenting almost a year following vaccination [15]. Vaccine-associated pneumonitis and encephalitis have also been described in non-HIV infected individuals who are severely immunocompromised. Serious illnesses have not been reported in HIV-infected individuals in association with mumps or rubella vaccine administration.

2.8 Contraindications
- A history of previous severe adverse reaction or allergy to the vaccine or its components.
- Persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated.
- Pregnancy. Pregnancy should be avoided for one month after vaccination). The vaccine is not contraindicated in breastfeeding women.
- Persons who are severely immunocompromised due to disease or treatment, including HIV-infected patients with CD4 < 200/mm³

2.9 Pre- and post-vaccination testing
Rubella-susceptible pregnant women are identified during routine antenatal screening. Serological screening for measles and rubella IgG to identify candidates for MMR vaccination is recommended in a variety of settings, including the occupational health setting and HIV infection. Rubella IgG tests are subject to internationally-agreed standards, but there are no agreed standards for measles or mumps serology.

3. Pre-exposure prophylaxis: Human Normal Immunoglobulin
HNIG affords short-lived protection against measles (about 3 weeks).

4. Recommendations for pre-exposure prophylaxis in HIV-infected adults
- HIV-infected persons should be screened for evidence of immunity to measles (C, IV). The MMR vaccine (two doses, with the second dose given at any time but at least one month after the first.) is recommended in Measles IgG seronegative asymptomatic or mildly symptomatic HIV-infected persons with CD4 counts >200 cells/mm³ (C, IV).
- HIV-infected women of child-bearing age should be also screened for rubella IgG (C, IV). Rubella seronegative women with CD4 count >200 cells/mm³ who are seropositive for measles, should be given one MMR dose (C, IV). 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 contra-indicated (C, IV).
- Administration of HNIG should be considered for severely immunocompromised (CD4 < 200 cells/mm³) HIV-infected patients who are measles IgG negative, immediately prior to travel to countries where measles is endemic, bearing in mind that any protection afforded will be short-lived (approximately 3 weeks) (C, IV).

5. Recommendation for vaccine use in close contacts of HIV-infected adults
MMR vaccinees do not act as a potential source of vaccine virus infection to their immunocompromised contacts [16]. The healthy close contacts of HIV–infected individuals should receive a two-dose MMR vaccine course unless there is adequate evidence of immunity [16, 14]. (C, IV)

6. Post-exposure prophylaxis: MMR vaccine
Due to the rapid induction of measles antibody, healthy contacts of measles may be protected by MMR vaccination administered within three days of exposure [16]. 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.

7. Post-exposure prophylaxis: Human Normal Immunoglobulin
HNIG can attenuate clinical measles in healthy contacts but efficacy is less well defined in the immunocompromised [17-18, 1]. Following exposure to measles, HNIG maybe given by intramuscular injection within 72 hours of exposure, but may be beneficial up to 6 days. Intravenous immunoglobulin (0.2g per kg body weight) could be considered instead for persons in whom intramuscular injections are contraindicated. There is no evidence to support the use of HNIG to prevent infection following exposure to mumps or rubella.

8. Recommendations for post-exposure prophylaxis in HIV-infected adults
- Following a high-risk contact with measles, the measles IgG serostatus should be determined, but prophylaxis should not be delayed pending test results.
- Post-exposure prophylaxis with NHIG should be started as soon as possible and at least within 5 days of exposure(C, IV). As neither prior vaccination, nor detectable measles IgG ensures protection in the immunocompromised, administration of HNIG after a high-risk contact is recommended for all HIV-infected persons regardless of vaccination or measles IgG serostatus (C, IV).
- HNIG should be considered for susceptible (IgG seronegative) pregnant women exposed to rubella or measles (C, IV)

9. Auditable outcomes
Screen HIV-infected persons for evidence of Measles IgG (target 90%)
Screen HIV-infected women of childbearing age for evidence of Rubella IgG (target 75%)
Offer MMR vaccination to measles and/or rubella seronegative HIV patients who are neither pregnant nor severely immunocompromised (target 90%).

References


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1. Background

1.1 Neisseria meningitidis

*N. meningitidis* is a gram-negative bacterium. There are at least 13 serogroups. Clinically important serogroups include A, B, C, Y and W135.

1.2 Clinical features

*N. meningitidis* is a common and frequently devastating cause of meningitis and septicaemia, particularly in children and young adults. 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.

1.3 Epidemiology

Serogroups B and C are the commonest serogroups isolated in the UK, rest of Europe, the Americas, Australia and New Zealand. An effective Group C conjugate vaccine is available to prevent infection with serotype C. Since the introduction of the vaccine in the late 1990s in the UK for routine infant immunisation, 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.

1.4 Transmission

Humans are the only known reservoir for *N. meningitides* and between 5% and 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.

1.5 Incubation period

2-7 days.

1.6 Risk groups

It is not fully understood why the disease develops in some individuals but not in others. Household contacts of cases of meningococcal infection are at increased risk of developing the disease. Persons who have deficiencies in the terminal common complement pathway (C3, C5--9) and those with anatomic or functional asplenia are also at increased risk for acquiring meningococcal disease. Antecedent viral infection, household crowding, chronic underlying illness, and both active and passive smoking also are associated with increased risk for meningococcal disease [1]. During outbreaks, bar or nightclub patronage and alcohol use also have been associated with higher risk for meningococcal disease [1]. Travellers to endemic and epidemic 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.

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

- persons who travel to or reside in countries in which \( N. meningitidis \) is hyperendemic or epidemic, particularly if contact with the local population will be prolonged
- college students living in dormitories
- 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

1.7 Meningococcus in HIV-infected persons
There is no evidence that infection by \( N. meningitidis \) is more common in HIV infected individuals [2,3], although patients with lower CD4 counts may be more susceptible to less pathogenic strains of meningococci [4].

2. Pre-exposure prophylaxis: Meningococcus vaccine

2.1 Vaccine composition
In the UK there are several Group C conjugate vaccines (MenC) available and one quadrivalent vaccine (ACWY Vax) [5]. The MenC vaccine contains Group C oligosaccharide conjugated to either diphtheria or tetanus protein, adsorbed on aluminium hydroxide. MenC is recommended for all routine immunisations. The quadrivalent polysaccharide vaccine contains A, C, W135 and Y polysaccharide and 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.

2.2 Route of administration
The vaccine is given by deep subcutaneous or intramuscular injection, preferably in the deltoid.

2.3 Schedule of administration in the general population
MenC has been used for routine childhood vaccination in the UK since 1999, and is also recommended for non-immune first-year college and university students aged 20-24. In adults the vaccine is given as a single dose. Persons with asplenia or splenic dysfunction should receive two doses two months apart [5].

The ACWY vaccine is recommended for those travelling to or living in epidemic regions of the world. Proof of vaccination with the quadrivalent vaccine is required for visitors arriving in Saudi Arabia for the Hajj and Umrah pilgrimages. The vaccine not
recommended for travellers to areas outside of Africa (other than Saudi Arabia during the Hajj / Umrah) unless outbreaks occur. In adults the vaccine is given as single dose.

2.4 Vaccine efficacy in healthy individuals
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 [6,7]. More recently the immunogenicity (which is established as a surrogate of clinical efficacy) of conjugate vaccines has been demonstrated in children [8,9]. 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 late 1990s in the UK, cases of Group C disease have declined dramatically [10,11]. The protection afforded by the vaccines is strictly serogroup-specific.

2.5 Vaccine efficacy in HIV-positive persons
There has been very little 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 [12-14]. The UK Department of Health does not consider HIV infection a contraindication to vaccine use [5].

2.6 Duration of protection
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 to 5 years. Boosters are recommended after 5 years for those at continuous risk. The duration of protection may be reduced in HIV-infected persons, but there is insufficient evidence to modify standard boosting recommendations.

2.7 Adverse events
Fever and injection site reactions are the most common adverse events reported. More serious (neurological) complications or anaphylaxis are very rare.

2.8 Contraindications
1. A history of previous severe adverse reaction or allergy to the vaccine or its components (including diphtheria toxin for the conjugate vaccine).
2. Persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated.
3. Meningococcal vaccines may be given to pregnant women when clinically indicated.

3. Recommendations for pre-exposure prophylaxis in HIV-infected adults
- In agreement with current national guidelines, MenC vaccination (one dose) is recommended in all HIV-infected young adults <25 years of age who have not previously received the vaccine or have uncertain immunisation history (BIII). 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 (BIII), including those who have previously received MenC vaccination. The vaccine should be considered for a) travellers who will be living or working with local people in an area of risk, b) for long stay and rural travellers visiting areas of risk, c) as backpackers, and d) travellers visiting an area of risk during an outbreak. These persons should receive one vaccine dose. If the risks recur 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).

Responses to the vaccine may be reduced in patients with CD4 counts <200 cells/mm$^3$. If vaccination is indicated in a HIV-infected person, re-immunisation should be considered after HAART-induced immunoreconstitution (C, IV).

4. Passive immunoprophylaxis
None recommended

5. Post-exposure prophylaxis
Contacts of confirmed cases of serogroup A, C, W135 or Y meningococcal disease should be offered vaccination, as well as given chemoprophylaxis, as recommended in current guidelines [5]. The recommended schedule for prophylaxis is 600mg of rifampicin every 12 hours for two days in adults. Ciprofloxacin (500 mg once) may be used as an alternative in patients on antiretroviral therapy. Rifampicin 600 mg twice daily for two days or intramuscular ceftriaxone 250 mg should be given to pregnant contacts [5].

6. Auditable outcomes
Documented administration of Men C vaccine in recommended groups (target 90%) and quadrivalent vaccine in travellers (target 90%).

References

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• **Conflict of interest:** Lecturing fees from Aventis Pasteur
Pertussis (Whooping Cough)

1. Background

1.1 Bordetella pertussis
Whooping Cough is a highly contagious disease of the respiratory tract usually caused by the bacterium *B. pertussis*. A similar illness can also be caused by *B. parapertussis* but this is not preventable with currently available vaccines.

1.2 Clinical Features
Pertussis ranges from a mild disease to one that is serious and can result in death. The illness progresses from a catarrhal stage with symptoms that may be similar to a common cold, to an irritating cough that gradually becomes paroxysmal. The paroxysms are often followed by a characteristic ‘whoop’ which may be accompanied by vomiting. The coughing episodes are exhausting leading to difficulty in eating, drinking and breathing. The illness commonly lasts 6-8 weeks even when treated with antibiotics, and may be complicated by bronchopneumonia, severe weight loss or cerebral hypoxia leading to brain damage. Minor complications include epistaxis, otitis media and subconjunctival haemorrhages.

1.3 Epidemiology
Prior to the introduction of the pertussis vaccine in the U.K in the 1950s, pertussis epidemics occurred every 3-4 years with the average annual number of notifications in UK exceeding 120,000. In 1972, when vaccine acceptance was over 80%, there were only 2,069 notifications of pertussis. Due to diminished public confidence in the safety and efficacy of the vaccine in 1975 immunisation coverage dropped to 30% resulting in more than 200,000 extra notifications and 100 deaths during the 1970s and 1980s. Vaccine coverage steadily increased over the next decade, and 1995 vaccine coverage reached 94% where it has consistently remained to date. Correspondingly, notifications decreased dramatically during this period with 2003 being the lowest total on record [1]. The incidence of disease is now at an all time low, and there has been no epidemic in any age group since 1997. Despite current low levels of the disease, pertussis remains a significant cause of illness and death in young infants under 1 year of age.

Immunisation or infection with pertussis does not induce life long immunity and in recent years, it has become evident that pertussis continues to circulate among older children and adults creating a source of infection for younger children. Although an encouraging reduction in incidence has been seen in the last two years, following the addition of pertussis vaccine to the pre-school routine booster, the possible need for an additional pertussis booster for adolescents and adults in the future is currently under review [2].

1.4 Transmission
The disease is transmitted easily from an infected person via airborne droplets produced when coughing or sneezing. Cases are infectious from six days after exposure to three weeks after onset of cough.
1.5 Incubation period
6-20 days.

1.6 Risk groups
Young infants and children under the age of 1 year are most at risk of severe complications from pertussis. Adults, older children and those partially protected by vaccination may still become infected but usually have milder disease often indistinguishable from upper respiratory tract infection. They may transmit the disease to other susceptible persons and are often found to be the index case in a household with multiple cases.

1.7 Pertussis in HIV-infected persons
Pertussis has been diagnosed in HIV infected adults and children and should be considered as a cause of respiratory disease in persons with HIV [3-5]. Current studies however do not suggest that pertussis is a common infection among persons with HIV or indeed that they are more likely to be a reservoir for *B. Pertussis* in the community [6].

2. Pre-exposure prophylaxis: Pertussis vaccine

2.1 Vaccine composition
All currently available pertussis vaccines licensed in the UK are inactivated acellular vaccines made from highly purified selected components of *B. pertussis*: between two and five components are commonly used. These are treated with formaldehyde or glutaraldehyde and then adsorbed on to an adjuvant, either aluminium phosphate or aluminium hydroxide. Whole cell pertussis vaccines are no longer available in the UK.

There are no pertussis-containing vaccines currently licensed in the UK for primary vaccination of persons over 10 years of age. A preparation combining five component 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. Acellular pertussis booster vaccines formulated specifically for adolescent and adults are available in Australia, Canada, France and Germany, and recommended for those who have completed a full primary course of pertussis in childhood.

2.2 Route of administration
The pertussis vaccine is given by intramuscular injection (or subcutaneous injection in persons with bleeding disorders), preferably in the deltoid. The vaccine must not be administered by the intradermal or intravenous routes.

2.3 Schedule of administration in the general healthy population
Pertussis vaccine is only currently recommended in the UK for the routine immunisation of children aged two months to 10 years. A primary course of pertussis consists of 3 doses of pertussis-containing vaccine administered at least one month apart. Pertussis vaccination in individuals aged 10 years and over is not currently recommended in the UK.
2.4 Vaccine efficacy in healthy individuals
Acellular pertussis vaccines are known to be safe and immunogenic in immunocompetent adults [7]. Currently available acellular pertussis vaccines differ in source, number and amount of components, and method of manufacture, resulting in differences in efficacy. Overall the vaccines are estimated to have a clinical efficacy against severe disease ranging from 75% to 90% [8]. 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.

2.5 Vaccine efficacy in HIV-positive persons
Toxoid vaccines are known to be adequately immunogenic in a variety of immunocompromised hosts [9]. No data on the clinical efficacy of the pertussis vaccine in HIV-infected adults is available at this time. A study of HIV-infected children showed protective serological response in 6 of 12 children after a primary vaccine series. Antibody titres were lower in comparison with HIV-negative age-matched controls. Protective antibody response correlated with the CD4 count [10]. Patients in the earlier stages of infection are more likely to mount a protective antibody response than those with HIV related symptoms thus vaccination early in the course of disease, or after immune reconstitution on HAART, is more likely to produce a better serological response [11]. As a general rule the lower the patients CD4 count the less likely they are to show vigorous response to vaccination [12].

2.6 Duration of protection
The duration of protection is unknown. Children under 10 years should receive a pertussis booster ideally 3 years after the primary course. Booster doses are not currently recommended in children over 10 years of age and adults.

2.7 Adverse events
Pain swelling and redness at injection site are common side effects of 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 [13, 14] pertussis vaccination may induce transient increases in HIV plasma RNA load, but has not been shown to lower CD4 cell count or have a negative effect on HIV-1 progression [15-17].

2.8 Contraindications
- A history of previous severe adverse reaction or allergy to the vaccine or its components.
- Persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated.

2.9 Pre- and post-vaccination testing
Not recommended
3. Recommendation for pre-exposure prophylaxis in HIV-infected adults

- Pertussis immunisation in individuals aged 10 years and over is not recommended in the UK schedule and currently there is no licensed available vaccine recommended for this use.
- In circumstances where a previously unvaccinated adult requires a full primary course of vaccination with diphtheria, tetanus and polio, the option of offering a combination which contains low-doses of pertussis antigens could be considered. Although this may not provide good levels of protection, the use of a combined vaccine containing pertussis would not be expected to increase side effects (C, IV).
- For individuals at high risk of infection (for example those exposed in the house-hold or in high risk occupations) a single additional dose of a pertussis containing vaccine could be considered (C, IV). Such additional doses are unlikely to produce unacceptable rates of reaction but the level of protection offered is currently unknown and may be limited with currently available vaccines.

4. Passive immunoprophylaxis

None recommended

5. Post-exposure prophylaxis

Unimmunised or partially immunised individuals and vulnerable close contacts of a case of pertussis should be offered antibiotic prophylaxis within 21 days of onset of clinically suspected or confirmed case [18]. The recommended regimen for antibiotic prophylaxis for adult close contacts is oral erythromycin (250-500mg 6 hourly) for 7 days. Erythromycin is the only antibiotic shown to have any prophylactic effect on pertussis. *B. Pertussis* is sensitive to a wide range of antibiotics and chlarythomycin may be considered as an alternative. There is no evidence concerning the efficacy of antibiotic prophylaxis in HIV-infected persons. Review of experimental and analytical studies concluded use of post exposure prophylaxis should be confined to vulnerable and close contacts of cases due to its limited benefit [18].

6. Recommendations for post-exposure prophylaxis in HIV-infected adults

- Pertussis post exposure prophylaxis is recommended in all HIV-positive persons regardless of CD4 count or immunisation status and should be given in accordance with the standard recommendations (see section 5) (C, IV).

7. Auditable outcomes

Documented completion of primary vaccination (Target 75%).
References


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Pneumococcus

1. **Background**

1.1 *Streptococcus pneumoniae*

*S. 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.

1.2 **Clinical features**

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 presence of other infections of the respiratory tract. Pneumococci can cause the following types of disease: a) invasive pneumococcus disease (IPD), including bacteraemia and meningitis; b) pneumonia and other lower respiratory tract infections; and c) upper respiratory tract infections, including otitis media and sinusitis [1]. Meningitis is frequently complicated by neurological sequelae.

1.3 **Epidemiology**

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.

1.4 **Transmission**

Infection is acquired though direct person-to-person contact via respiratory droplets and by autoinoculation in persons carrying the bacteria in their upper respiratory tract.

1.5 **Incubation period**

1-3 days for pneumonia

1.6 **Risk groups**

The mechanisms that control the healthy carrier state versus invasive disease are not understood. 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 older adults (≥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
• immunocompromise due to disease or treatment, including HIV infection

1.7 Pneumococcus infection in HIV-infected persons
Pneumococcus infection is a significant cause of pneumonia and IPD in HIV-infected persons [2]. Disease can occur early in the course of HIV infection and may recur. Paediatric serotypes are frequently involved and close contact with children is a recognised risk factor for infection [3]. Risk factors for severe disease include low CD4 count, African race, HIV acquired via blood transfusion or intravenous drug use, previous AIDS-defining opportunistic infections, previous pneumonia and alcoholism [4]. The annual attack rate of pneumococcal bacteraemia is as high as 1% among persons with AIDS [5]. Compared with 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 count. Among hospitalised persons, the mortality rates are approximately 20% for pneumonia, 26% with bacteraemia without localising signs and 65-75% for meningitis. The risk of antibiotic resistance is higher in HIV-infected persons than HIV-negative persons [6]. Acute pneumococcal pneumonia itself can depress the CD4 count [7].

Since the advent of HAART the incidence of IPD has declined in the developed world [8, 9]. Major risk factors for IPD in the HAART era are similar to those reported in HIV-negative individuals and include associated comorbidity, alcoholism, prior hospitalisation, current smoking and CD4 <100 cells/mm$^3$ [9]. Despite these improvements however the incidence of IPD remains substantially higher in HIV-positive persons than in similarly aged HIV-negative adults [10].

2. Pre-exposure prophylaxis: Pneumococcus vaccine

2.1 Vaccine composition
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 immunisation 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 additional 8% cases of IPD.

2.2 Route of administration
PPV-23 is given by subcutaneous or intramuscular injection, preferably into the deltoid.

2.3 Schedule of administration in the general population
PPV-23 is given as a single dose.

2.4 Vaccine efficacy in healthy individuals
More than 80% of healthy young adults who receive PPV-23 develop antibodies against the serotypes contained in the vaccine, usually within 2 to 3 weeks after vaccination [1]. In older adults and persons with underlying conditions responses are often reduced or
absent. The levels of antibodies that correlate with protection against pneumococcal disease have not been clearly defined.

Overall, PPV-23 is estimated to be 60%–70% effective in preventing IPD, but may be less effective in those groups that have also the greatest risk of disease [1]. PPV-23 efficacy against non-bacteraemic pneumonia has not been unequivocally demonstrated. The original clinical efficacy trial performed in the ‘70s in young healthy South African gold miners demonstrated a significant reduction in radiologically-proven pneumonia among vaccine recipients. However, in a meta-analysis of 9 randomised controlled trials vaccination appeared to be only efficacious in reducing bacteraemic pneumococcal pneumonia in low-risk adults. The review failed to demonstrate vaccine efficacy for non-bacteraemic pneumonia and among persons in high-risk groups [11]. More recently, the use of CPV has shown efficacy in children in reducing the risk of IPD by 60-65% [12] and the risk of clinical lower respiratory tract disease by 15% [13]. In addition vaccinated children also showed a reduced risk of influenza-related hospitalisation [14].

2.5 Vaccine efficacy in HIV-positive persons
HIV-infected persons may have a diminished antibody response to pneumococcal vaccine and the reduction corresponds to the degree of immunodeficiency [15-18]. Responses are often lower in HIV-infected patients with CD4 counts <500 cells/mm³ than in those with higher CD4 counts [18]. HAART is expected to improve responses to vaccination, but responses may remain suboptimal, even after re-vaccination [19-21]. A prime-boost approach using a CPV vaccine initially, followed by PPV-23 boosting appears to improve responses in children [22], but there are no data for adults.

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 or receiving suboptimal mono and dual therapy. In the only randomised controlled trial, the vaccine showed no efficacy in reducing the risk of pneumococcal disease among Ugandan HIV-infected persons not taking antiretroviral therapy [23]. Surprisingly there was a borderline increase in pneumonia due to any cause in vaccine recipients (Hazard Ratio 1.89, 95% confidence interval 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 [24]. No satisfactory explanation has been provided for these findings. However, several observational studies conducted in the United States 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 [25]. One large prospective multi-centre observational study in the United States demonstrated a reduced incidence of pneumococcal disease in vaccine recipients with CD4 counts >500 cells/mm³, but not in those with lower CD4 counts [4]. Three further retrospective case-control studies also showed varying efficacy of the vaccine, depending on race and CD4 count [3, 26, 27].

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

73
opportunistic infections [28]. In a Spanish prospective study, the odds ratios for developing pneumococcal pneumonia and IPD were 0.23 (95% confidence interval, CI 0.008-1.06) and 0.14 (95% CI 0.02-1.2) respectively in vaccinated persons relative to unvaccinated persons [29].

The UK Department of Health recommendation for pneumococcal vaccination includes HIV infection at all stages [30]. American guidelines recommend vaccination for those with CD4 counts >200 cells/mm$^3$ and indicate that vaccination should also be considered for patients with CD4 <200 cells/mm$^3$, although there is no clinical evidence for efficacy [25].

### 2.6 Duration of protection

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. Re-vaccination after 5-10 years of the first dose may be considered in high-risk groups in whom antibody levels are likely to decline [30].

### 2.7 Adverse events

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

In HIV-infected persons, a transient increase in plasma HIV RNA load has been observed following administration of PPV-23 [31]. No clinical or immunologic deterioration has been reported in these persons.

### 2.8 Contraindication

- A history of previous severe adverse reaction or allergy to the vaccine or its components.
- Persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated.
- Pregnancy or breastfeeding. No adverse consequences have been reported among newborns whose mothers were inadvertently vaccinated during pregnancy.
- Vaccination given within the previous 3 years [30]. However, when indicated, vaccine should be administered to patients who are uncertain about their vaccination history.

### 2.9 Pre- and post-vaccination testing

Not generally recommended
3. Recommendation for 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/mm³, 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/mm³ who are stable on HAART (C, IV).

- Given the increased risk for disease, vaccination may be considered for HIV-infected persons with CD4 count <200 cells/mm³ (C, IV).

- Vaccine failures should be monitored and reported.

- In all patients, the indications for vaccination are strengthened in the presence of additional risk factors (C, IV).

- In persons who received the vaccine when the CD4 count is <200 cells/mm³, re-vaccination should be considered following HAART-induced CD4 count increase >200 cells/mm³ (C, IV).

4. Passive immunoprophylaxis

None recommended

5. Post-exposure prophylaxis

None available

6. Auditable outcomes

The proportion of adults receiving this vaccine with CD4 counts >200 cells/mm³.

References


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1. Background

1.1 Polioviruses
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 characterised by neuro-invasiveness.

1.2 Clinical Features
The majority of infections are sub-clinical, but a minority give rise to neurological manifestations including aseptic meningitis, encephalomyelitis and the poliomyelitis syndrome, characterised by the acute onset of flaccid paralysis. The live attenuated oral polio virus vaccine (OPV) is asymptomatically shed in the stool of vaccinees for several days and shedding may be prolonged in immunocompromised persons [1-3]. The vaccine viruses can rapidly revert to virulence and may give rise to vaccine-associated paralytic polio (VAPP) in vaccinees or in their contacts [1, 4].

1.3 Epidemiology
As a result of continuing efforts to interrupt wild polio virus transmission, poliomyelitis continues to occur in only a few countries. Poliomyelitis 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.

1.4 Incubation Period
3 to 21 days.

1.5 Transmission
Polioviruses are spread by the faecal-oral and respiratory routes.

1.6 Risk Groups
Susceptible adults may be at greater risk of paralytic polio than children. The estimated ratio of unapparent to paralytic infections is 75 to 1 in adults and 1000 to 1 in children [1]. Following OPV vaccination, immunocompromised persons are at greater risk of developing VAPP than healthy individuals [1, 4]. Patients with hypogammaglobulinaemia have the greatest risk, but VAPP has also been reported in children with HIV infection [4-6].

1.7 Poliovirus infection in HIV-infected persons
There are no specific data available on wild-type poliomyelitis in HIV-infected persons.
2. Pre-exposure prophylaxis: Polio vaccine

2.1 Vaccine composition
The OPV, comprising live attenuated strains of the three poliovirus subtypes, is no longer routinely available in the UK having been replaced in 2004 with the enhanced inactivated poliovirus vaccine (IPV) in all routine vaccine schedules. IPV contains the three serotypes of formaldehyde-inactivated poliovirus grown on monkey kidney cells. The efficacy of current IPV is greater than that of the original Salk IPV introduced in the 1950s, and comparable to that of OPV [1]. Unlike OPV, which is contraindicated in patients with HIV, IPV it can be safely administered to profoundly immunocompromised adults [1, 7]. 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).

2.2 Route of administration
The vaccine is given by intramuscular (or deep subcutaneous injection in case of bleeding disorders), preferably in the deltoid.

2.3 Schedule of administration in the general healthy population
Five doses of a polio-containing vaccine are recommended for routine childhood vaccination in the UK: 3 doses are administered at 2, 3 and 4 months of age, with a first booster pre-school, and a second booster ten years after the first [1]. In adults, the recommended schedule is three IPV doses at 0, 1 and 2 months, followed by 2 additional doses after 5 and 10 years [1]. Any combination of OPV and IPV can constitute a complete series [1].

2.4 Vaccine efficacy in healthy individuals
OPV and IPV both induce virus-neutralising 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 [8].

2.5 Vaccine efficacy in HIV-positive persons
Both OPV and IPV can elicit neutralising antibody responses in HIV-infected children [4]. 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 neutralising antibody to all three serotypes after two doses of IPV, and 100% to at least two serotypes [9]. However, responses were reduced in children with more advanced disease [9, 10].

The seroprevalence of poliovirus neutralising antibodies varies among HIV-infected adults. High prevalence rates, comparable to those in normal controls, have been reported in some cohorts [11, 12]. In a seroepidemiological study of Italian drug addicts
however, those with HIV infection were more likely to lack protection, with 34% seronegative for poliovirus type 1, and 11% lacking neutralising antibodies to all three virus types [13].

In the pre-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 [11, 12, 14]. However antibody titres were generally lower in vaccinated HIV-positive individuals than in HIV-negative persons [12]. Responses were especially impaired in symptomatic individuals [12], and in those with CD4 counts <300 cell/mm³ [11, 14]. Presumably humoral immune responses to IPV are restored in patients with advanced disease who are successfully treated with HAART [15].

2.6 Duration of protection
OPV is likely to confer life-long immunity. The duration of immunity conferred by IPV is not known, but in general, childhood immunisation 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 [8]. However, the longevity of protection may be reduced in HIV-infected patients.

2.7 Adverse events
Injection site reactions are the most common adverse events reported, occurring with greater frequency after subsequent doses. The IPV vaccine is safe in HIV-infected individuals. Whether vaccine administration may impact on HIV plasma viral load remains controversial but the impact is unlikely to be clinically significant [7, 16].

2.8 Contraindications
- A history of previous severe adverse reaction or allergy to the vaccine or its components.
- Persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated.
- There is no evidence of risk from vaccinating pregnant women or those who are breast-feeding with IPV and the vaccine may be given when clinically indicated.

2.9 Pre- and post-vaccination testing
None generally recommended in healthy individuals. Post-vaccination serology may be indicated in selected HIV-infected individuals (see below).

3. Recommendations for pre-exposure prophylaxis in HIV-infected adults
- HIV-infected patients born and resident in the UK since 1962 have generally received a complete 5-doses course of vaccination as part of routine childhood immunisation. 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 immunised. In the absence of a reliable history of vaccination, the opportunity to immunise them should not be missed. These patients should receive 5 IPV doses (C, IV).
• HIV-infected patients of any age and origin lacking a reliable history of vaccination should be offered 5 IPV doses (C, IV).
• Where indicated, the 5 doses should be administered as a primary course (3 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 5-doses vaccination course, regardless of the interval since the last dose and type of vaccine previously received (C, IV).
• Some HIV-infected persons with advanced disease and CD4 counts <300 cells/mm$^3$ may not make a full antibody response to vaccination. In these patients, consideration should be given to either delaying immunisation or repeat immunisation following HAART-induced immunoreconstitution (C, IV).
• HIV-infected patients who have completed a 5-doses 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 count <300 cells/mm$^3$, antibody levels should be determined against the three poliovirus serotypes four 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 count >300 cells/mm$^3$ should be offered a single reinforcing dose every 10 years (see section 2.6) (C, IV). Further boosting doses should be considered in HIV-infected persons with CD4 <300 cell/mm$^3$ 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).

4. Post-exposure prophylaxis: Normal Human Immunoglobulin
Normal Human Immunoglobulin (NHIG) 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. As 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 through close or household contact with OPV recipients vaccinated abroad, either in the UK or while travelling. There is no published evidence on the efficacy of NHIG in preventing or attenuating polio in immunocompromised individuals [17]. NHIG (750mg) is given by deep intramuscular injection in the anterolateral thigh [17]. Intravenous immunoglobulin (0.2g per kg body weight) could be considered instead for persons in whom intramuscular injections are contraindicated. NHIG should be given as soon as possible after exposure. Protection lasts for 3 weeks. Malaise, chills fever and rarely anaphylaxis have been reported.

5. Recommendations for post-exposure prophylaxis in HIV-infected adults
• NHIG is recommended for HIV-infected patients following exposure to wild-type polivirus or OPV, regardless of vaccination history (C, IV).
• 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. Serological testing is not however recommended to determine the need for NHIG.
• 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 need to be collected at weekly intervals for analysis. If poliovirus is detected, repeat administration of HNIG at three weekly intervals will be required until two consecutive stool samples test negative.

6. Auditable outcomes
Asses the vaccination history of HIV-infected patients and complete vaccination according to recommendations (Target 80%).

References


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• **Conflict of interest:** In the last five years, the author has received sponsorship from Aventis Pasteur MSD Ltd, towards the cost of conference attendance.
1. Background

1.1 Rabies virus
Rabies is caused by viruses of the Lyssavirus genus, including the classic rabies virus genotype 1 and other rabies-related viruses (e.g., European Bat Lyssaviruses, EBLV).

1.2 Clinical features
Rabies is an acute encephalomyelitis. In the prodromal period, fever, headache and malaise are often accompanied by pathognomonic paraesthesiae or pain at the wound site. The acute neurological period is characterised by hallucinations, seizures and maniacal behaviour, with furious episodes that are triggered by visual, auditory, or tactile stimuli (hydrophobia and aerophobia). This phase may end in cardio-respiratory arrest or progress to paralysis. Less commonly patients present with an ascending flaccid paralysis. In both furious and paralytic rabies, coma and death almost invariably follow. Five cases of survival have been documented in individuals with rabies who had previously received pre- or post-exposure prophylaxis. In October 2004 the first case of survival in the absence of any rabies immunisation was reported in a teenager with rabies who received an investigational regimen of antivirals and induced coma [1].

1.3 Epidemiology
Human rabies is common in most developing countries, where it occurs in both urban and rural areas [2]. The World Health Organisation (WHO) estimates that each year at least 55,000 people die from rabies in Asia and Africa, and of these Asia accounts for 56%. India alone reports 20,000 deaths per year [3]. Over 99% of all deaths occur in Asia, Africa and Latin America. In the majority of industrialized countries, human rabies is under control, mainly due to oral vaccination of wildlife and mandatory vaccination of domestic animals [4]. No case of indigenous human rabies from terrestrial animals has been reported in the UK since 1902. The first indigenous human case of rabies caused by EBLV-2 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. Wild mammals such as racoons, skunks, foxes, and insectivorius bats in North America; vampire bats and mongooses in Central America; jackals, hyenas and mongooses in Africa; wolves, foxes and insectivorius bats in Europe; and fruit bats in Australia are rabies vector species. 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 Daubentons bats [5]. In Asia, Africa and parts of Latin America both stray and domestic dogs remain the principal host 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 due to exposure to dogs, usually in the form of bites.

Risk of rabies by country is provided below [6]. This list is not exhaustive and may become out of date. For updated information on rabies by country, see the WHO
No risk

Europe: Belgium, Cyprus, Denmark, Faroe Islands, Finland, France, Gibraltar, Greece, Iceland, Ireland, Italy (except the northern and eastern borders), Luxembourg, Malta, Netherlands, Norway (mainland), mainland Spain (excluding North African coast) and the Canary Islands, Portugal, Sweden and the United Kingdom.

Americas: Anguilla, Antigua & Barbuda, Bahamas, Barbados, Bermuda, British Virgin Islands, Cayman Islands, Dominica, Equatorial Guinea, French Antilles, Guadeloupe, Jamaica, Martinique, Montserrat, Netherlands Antilles, St Christopher & Nevis, St Lucia, St Martin, St Pierre & Miquelon, St Vincent & the Grenadines, Turks & Caicos, Virgin Islands, and Uruguay.

Asia: Bahrain, Brunei, Darussalam, Hong Kong, Japan, Kuwait, Maldives, Qatar, Singapore, Taiwan and United Arab Emirates.

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.

Low risk

Europe: Austria, Bulgaria, Czech Republic, Germany and Switzerland.

Americas: Canada, USA (see the CDC for information on the risk of rabies in different parts of the USA).

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’.

1.4 Transmission

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. It does not occur through intact skin. 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 8 cases transmitted through corneal grafts and 7 recipients of solid organ transplants from donors unsuspected of having rabies [7,8].

1.5 Incubation period
3 to 12 weeks (range 4 days to 2 years or more).

1.6 Risk groups
These include laboratory workers handling the virus, veterinarians, animal handlers, wildlife officers, persons who regularly explore or hike in caves, health care 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, although a risk for those handling bats has been recently recognised.

1.7 Rabies in HIV-infected persons
HIV-infected persons are at risk of rabies if they belong to a group at recognised 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. The vaccines contain modified live rabies virus or recombinant vaccinia-rabies glycoprotein virus, but adverse effects have very rarely been implicated in humans. As dogs are often attracted to the baits, dog owners should be aware that there may be an increased risk of adverse events in hosts with altered immunity.

2. Rabies vaccine
2.1 Vaccine composition
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. Other cell-culture-derived vaccines are available in some countries. Vaccines of nerve tissue origin are still in use in some developing countries. These are reactogenic and some are of low immunogenicity.

2.2 Route of administration
For both pre- and post-exposure prophylaxis, vaccine is administered by intramuscular injection (or deep subcutaneous injection in case of bleeding disorders), preferably into the deltoid region. The antibody response may be reduced if the gluteal region is used or the vaccine is injected into fat. Intradermal administration of smaller vaccine doses is used in some developing countries to reduce vaccination costs, but it may result in reduced immune responses [9, 10]. The vaccine must not be given intravenously.

2.3 Vaccine efficacy in healthy individuals
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
encephalitis, but delayed or incomplete treatment results in human deaths, often associated with severe lesions on or near the head or hand. Whether this equates to reduced protective efficacy remains unclear. High-dose steroids and radiation therapy may reduce vaccine efficacy.

2.4 Vaccine efficacy in HIV-positive individuals
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 count and disease stage, with low or absent antibody responses reported in some persons with CD4 counts <200-250 cells/mm³ [11-14]. In published studies, most vaccine failures occurred in persons who were either untreated or receiving suboptimal antiretroviral therapy. It is likely, although currently unproven, that HAART-induced immune reconstitution 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.

2.5 Duration of protection
In over 96% of healthy vaccine recipients, rabies neutralising antibodies persist for at least 10 years after primary pre-exposure vaccination with a cell vaccine followed by a single booster dose after one year. The duration of immunity in HIV-infected persons is unknown.

2.6 Adverse events
Although associated with mild and transient reactions, all the cell-derived rabies vaccines are considered safe [10, 15]. With HDCV, injection site reactions occur in 30%–74% of vaccinees within 24-48 hours 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 as with many other vaccines. In the few studies reported, the rabies vaccines were well tolerated in HIV-infected persons and did not cause significant changes in viral load or CD4 counts [11-14].

Inactivated vaccines produced in sheep or goat brains (Semple) or suckling mouse brain (Fuenzalida) are in use in some developing countries and may be offered to travellers exposed to animal bites in some countries such as Vietnam. They can be associated with serious and even fatal autoimmune neurological adverse events, including meningoencephalitis, myelitis, mononeuritis multiplex and ascending paralysis. 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.
2.7 Contraindications

Pre-exposure prophylaxis:
- A history of previous severe adverse reaction or allergy to the vaccine or its components.
- Persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated.
- Vaccine should only be given to pregnant women if the risk of exposure to rabies is high. Removal of pregnant woman from high-risk area if feasible may be preferred.
- Antimalarial chemoprophylaxis with chloroquine is contraindicated with intradermal vaccination.

Post-exposure prophylaxis:
- There are no absolute contraindications to rabies vaccine used for post-exposure prophylaxis. Hypersensitivity reactions can occur and caution is required in persons known to be sensitive to neomycin, amphotericin B, or chlorotetracline. 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 increased mortality noted in animal studies and because they reduce the response to the vaccine.

2.8 Pre- and post-vaccination testing

A rabies neutralizing antibody level >0.5 IU/ml is considered the minimal adequate response indicating unequivocal seroconversion [10]. 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: 01932341111; Website: www.vla.gov.uk).

3. Rabies Immunoglobulin

3.1 Composition

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.

3.2 Route of administration

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 as higher doses are associated with reduced antibody response to vaccine. Current guidelines indicate that if HRIG is not available until >7 days after vaccination has started, then it is probably unnecessary because an active antibody response has already begun. Delayed administration may still be indicated in immunocompromised persons. Rabies vaccine and immunoglobulin should not be given with the same syringe or in the same site.

3.3 Adverse events
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 (0.8-6%), which includes serum sickness but usually involves minor reactions.

3.4 Contraindications
Rabies immunoglobulin is never contraindicated in documented hypersensitivity, but adrenaline should always be at hand.

4. Recommendations for pre-exposure prophylaxis in HIV-infected adults

Travellers:
- Pre-exposure 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 count <200 cells/mm³ due to uncertainties about efficacy of post-exposure prophylaxis and most appropriate immunisation 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 as 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)
- Where there is a doubt about the efficacy of vaccination, post-vaccination serological testing to assess the antibody response to the primary vaccine course 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 re-checked (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 re-occurs, 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 immunocompromise, 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 vaccination. 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 as 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 count <400 cells/mm$^3$, nadir CD4 count <200 cells/mm$^3$, 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 re-checked (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 to 24 months depending on level of risk, to determine the need for booster doses (BIII)

5. Recommendations for post-exposure prophylaxis in HIV-infected adults

- Given the limited evidence, each case should be evaluated on its merits using serological testing and expert advice as a guide. Caution is required for patients with CD4 counts <200 cells/mm$^3$, those with nadir CD4 count <200 cells/mm$^3$, and those with currently or previously symptomatic disease, as responses to vaccination may be reduced. It is likely that HAART-induced immune reconstitution improves responses to vaccination.
- Post-exposure prophylaxis must be started as soon as possible after a suspected rabies exposure. As 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 thoroughly cleansed for a minimum of 5 minutes 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, see:
  - WHO: http://www.who.int/rabies/
  - 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 and appearance of the animal; vaccination status of the animal; the 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 health care workers is indicated only for high-risk exposures, including contamination of mucous membranes or open wounds by saliva, tears, cerebrospinal fluid, or neurological tissue.
- Vaccines of nerve tissue origin are not generally 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.
6. Schedule for post-exposure prophylaxis in HIV-infected adults

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Previously appropriately vaccinated and currently asymptomatic with CD4 &gt;400 cells/mm³ (see below(^a))</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound care: cleaning and leaving open</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>HRIG on day 0</td>
<td>No</td>
<td>Yes (see below(^b))</td>
</tr>
<tr>
<td>Intramuscular Rabies Vaccine(^c,d)</td>
<td>2 doses on days 0, 3</td>
<td>5 doses on days 0, 3, 7, 14, 30</td>
</tr>
<tr>
<td>Serological testing(^f)</td>
<td>After Day 14</td>
<td>After day 14</td>
</tr>
</tbody>
</table>

\(^a\)Every case should be judged on its merits. This category excludes persons who have received fewer than 3 vaccine doses previously, have uncertain vaccination history, had previous vaccination but showed an antibody responses <0.5 IU/ml, had CD4 count <400 cells/mm³ at the time of previous vaccination and no post-vaccine serological testing, are currently symptomatic, or have a current CD4 count <400 cells/mm³. If there is any uncertainty, a full post-exposure regimen should be given (B, III).

\(^b\)In countries classified as low risk, HRIG may not be required, but each case should be judged on its merits. Current guidelines indicate that if HRIG is not available until >7 days after vaccination has started, then it is probably 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 before (C, IV). Repeated doses of HRIG should not be administered once rabies vaccine treatment has been initiated to prevent interference with a maximum active immunity from rabies vaccine (C, IV).

\(^c\)All intramuscular injections must be given into the deltoid region. Vaccine should never be injected into the gluteal region

\(^d\)Some developing countries use economical multisite intradermal regimens for post-exposure vaccination. In these settings HIV-positive persons should preferably receive the standard intramuscular regimen (C, IV).

\(^e\)The abbreviated course is followed in some countries. It consists of 2 doses on day 0 (one in each deltoid), followed by one dose on day 7 and one dose on day 21.

\(^f\)Serological testing between day 14 and 28 is suggested in all HIV-positive persons and strongly recommended in those who have a CD4 count <200 cells/mm³ (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).

7. Auditable outcomes
Discuss rabies prophylaxis before travel to high-risk areas (Target 95%)
References


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Notes on Smallpox

1. Background
Smallpox is caused by Variola virus, a member of the orthopoxviridae family. There are two clinical variants: Variola major (mortality of up to 30%) and Variola minor (mortality of up to 5%). Smallpox 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.

Following a worldwide vaccination campaign, smallpox was declared eradicated from the world in 1980. The last known natural case occurred in Somalia in 1977. After the disease was eliminated from the world, routine vaccination against smallpox among the general public was stopped because it was no longer necessary for prevention. Vaccine programmes have recently been restarted in several countries in response to a hypothetical threat from bioterrorism [1, 2]. Several factors contribute to bioterrorism potential of the virus, including the high case-fatality rate, ready person-to-person transmission, lack of effective treatment and declining numbers of vaccinated people worldwide. In 2004-2005 efforts were made to offer vaccination to approximately 300 health care workers and ambulance staffing the UK to provide a front line response to a case of suspected smallpox. Laboratory workers are also vaccinated against this disease. If there were an outbreak of smallpox or significant concern, ring or mass vaccination may be undertaken for both the general public and health care workers.

2. Smallpox vaccine
The smallpox vaccine is a live vaccine that contains not the smallpox virus itself, but another virus known as the 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 that develops after 3-4 days. In healthy individuals 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.

3. Complications of vaccination
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 [2]. 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 is until the vaccination wound has healed and the scab has fallen off, usually within 14 to 21 days.

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

- Generalised vaccinia: characterised by a generalised rash; it 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: characterised by spread of vaccinia virus in eczematous skin with localised or generalised 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 characterised 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 <1/300 and related to CD4 count. There is one case report of progressive vaccinia in a military recruit who received smallpox vaccination in 1984 [3]. However, at least 350 other HIV-infected military recruits received the vaccine without known complications. In a study of 10 asymptomatic military recruits with a mean CD4 count of 483 (range 286-751) cells/mm³, the vaccine was well tolerated and induced a normal, robust response without complications [4]. Immune reconstitution with HAART is probably the best method to prevent vaccine-related complications.

In the past, high doses of vaccinia immunoglobulin (VIG) derived from immunised individuals appeared to be effective in halting a proportion of cases of progressive vaccinia. VIG was most effective in patients with less severe immunologic defects [5-8]. The experience with VIG for treatment of progressive vaccinia in persons with AIDS is limited to one reported case that occurred in 1984 [3].

4. Contraindications to vaccination
• A history of previous severe adverse reaction or allergy to the vaccine or its components.
• Persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated.
• Pregnancy and breastfeeding
• 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 immunocompromise due to disease or treatment, including HIV-infected persons [2].

5. Recommendations for HIV-infected adults
• All vaccine candidates should be made aware that the vaccine may pose a risk to people with HIV. HIV testing should be made available to those who wish to be tested prior to vaccination, although it should not be mandatory (C, IV).
• Where vaccination is being proposed for a HIV-infected person, a risk-benefit assessment should be made of the risk of contracting smallpox versus the risk of vaccine-related side effects. In the absence of recognised 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 (see section 3) (C, IV).

References

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Conflict of interest: None

Tetanus
1. Background

1.1 Clostridium tetani
Tetanus is an acute disease caused by the action of a toxin released by the gram-positive, anaerobic bacterium C. tetani. The bacterium produces two exotoxins, tetanolysin and tetanospasmin. Tetanospasmin is a neurotoxin responsible for the clinical manifestations of tetanus. C. tetani and its spores are found primarily in the soil and intestinal tracts of animals and humans.

1.2 Clinical features
In its most common manifestation, the disease is characterised by generalised 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%.

1.3 Epidemiology
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 of tetanus are reported in the UK each year. Until recently, most cases have been in elderly unvaccinated individuals. A recent increase in cases in intravenous drug users has been observed.

1.4 Transmission
Transmission occurs when spores are introduced into the body, typically through puncture wounds, burns and scratches, but also through trivial, unnoticed wounds, through injecting drug use, and occasionally through abdominal surgery. Tetanus spores are widely distributed in soil or manure and may be easily introduced into a wound 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.

1.5 Incubation period
The incubation period is usually 4-21 days, but may range from one 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.

1.6 Risk groups
Tetanus has only rarely occurred 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 greater than or equal to 60 years of age may lack protection.

1.7 Tetanus in HIV-infected persons
It is not known whether the natural history of tetanus is modified by HIV infection.

2. Pre-exposure prophylaxis: Tetanus vaccine
2.1 Vaccine composition
The vaccine is made from cell-free purified toxin extracted from C. tetani, treated with formaldehyde and converted into tetanus toxoid. This is adsorbed on to an adjuvant, either aluminium phosphate or aluminium hydroxide, to improve immunogenicity.

Tetanus vaccine is given to adults generally as part of a combined vaccine with low-dose diphtheria and inactivated polio (Td/IPV). This preparation contains a lower dosage of diphtheria toxoid than other similar preparations designed for use in childhood. Single antigen tetanus vaccine (T) and tetanus/low-dose diphtheria (Td) have been replaced by the combined Td/IPV for adults and adolescents for all routine uses in these age groups.

2.2 Route of administration
The vaccine is administered by intramuscular injection (or subcutaneous injection in persons with bleeding disorders), preferably in the deltoid. The vaccine must not be administered via the intradermal or intravenous routes.

2.3 Schedule of administration in the general healthy population
A primary course of tetanus consists of 3 doses of vaccine administered at least one month apart [1]. A booster dose should be given 5 years after primary course and a further booster 10 years later (making a total of 5 doses). There is no need to restart a series if more than the recommended time between doses has elapsed.

2.4 Vaccine efficacy in healthy individuals
Efficacy of tetanus vaccine has never been studied in randomised trials, although effectiveness has been extensively demonstrated by field use in the military [2]. Antitoxin antibody levels measured following vaccination also infer that the vaccine is highly effective. Studies in healthy infants have shown that following a primary course of 3 appropriately spaced vaccine doses, virtually 100% achieve antitoxin levels greater than the minimal protective level of 0.01IU/ml [3]. Studies in adults have demonstrated that although antitoxin levels decreases with age, the majority of vaccinated adults maintain protective antitoxin levels for many years [4].

2.5 Vaccine efficacy in HIV-positive persons
Tetanus vaccine has been shown to be adequately immunogenic in a variety of immunocompromised hosts [5,6]. Efficacy data in adults with HIV infection are limited. Studies in HIV-infected children have shown serological responses rates of 60% to 100% after a primary series of Tetanus/Diphtheria vaccination and 75% to 90% after booster vaccination [7]. Although these children show lower serum concentrations of diphtheria and tetanus antibodies compared with age-matched 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 several years after previous vaccination and are likely to develop protective levels of antitoxin following a booster dose [8]. Patients in the earlier stages of infection are more likely to mount a protective antibody response than those with HIV-related symptoms. Vaccination early in the course of disease is therefore more
likely to produce a better serological response [9]. As a general rule, responses are inversely correlated to the CD4 [10].

2.6. Duration of protection
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 individuals who are travelling to remote areas and may not therefore be able to receive tetanus immunoglobulin in the event of a tetanus prone injury. Antibodies in HIV-infected persons may decline to non-protective levels as immune function deteriorates [11].

Recovery from tetanus may not result in immunity, and vaccination following tetanus is indicated.

2.7 Adverse events
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. No increased risk of side effects or adverse reactions in individuals with HIV infection [12].

2.8 Contraindications
• A history of previous severe adverse reaction or allergy to the vaccine or its components.
• Persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated.
• The vaccine should not be used in pregnancy unless there is a significant risk of infection.

2.9 Pre- and post-vaccination testing
Not recommended.

3. Recommendation for pre-exposure prophylaxis in HIV-infected adults
• Tetanus toxoid vaccination is recommended in all HIV-positive persons regardless of CD4 count and should be given in accordance with standard recommendations (C, IV). Adults who have not previously been immunised or have an uncertain vaccination history require a full primary course (3 doses) in order to confer adequate protection. Further boosting doses should be planned at 5 and 10 years. Adults who have received a full primary course (3 doses) as an infant and a booster at pre-school age (total of 4 doses) require a single booster dose (C, IV).
• It seems wise to ensure that primary vaccination is completed in the early stages of disease or when the disease is well controlled on treatment. This avoids the need to consider vaccination when an adequate immune response is less likely (B, III). For those who receive the vaccine when their CD4 count is <200 cells/mm$^3$, a booster dose should be considered after HAART-induced immunoreconstitution (C, IV).
• As for healthy individuals, person who have received a full (5 doses) vaccine course require a booster dose at 10 yearly intervals if at risk of exposure (C, IV)

4. Passive immunoprophylaxis
None available

5. Post-exposure prophylaxis
Tetanus immunoglobulin (TIG) is used for post-exposure prophylaxis of tetanus following a possible exposure. TIG should be given by intramuscular injection in the deltoid within 24 hours of possible exposure. It is not indicated for persons who have received a dose of the vaccine within the previous 10 years. However, for individuals with a high risk wound who are severely immunosuppressed and unlikely to achieve and maintain protective levels of tetanus anti-toxin, TIG should be considered at the time of a tetanus-prone wound even where a dose of vaccine was received within the last 10 years. TIG confers protection for approximately 4 weeks [13].

In unvaccinated persons, tetanus vaccine alone is not considered adequate for post exposure prophylaxis after a high-risk exposure since vaccine given at the time of injury may not boost immunity early enough to give protection. TIG has not been studied in large scale trials. Evidence of its efficacy has been drawn from retrospective studies in HIV negative individuals. Efficacy of tetanus immunoglobulin in HIV-infected persons has not been established.

Wound cleaning, debridement when indicated, and proper immunization are the essential important components of wound management. The need for tetanus vaccine and TIG depends on both the condition of the wound and the patient's vaccination history. Patients with unknown or uncertain previous vaccination history and those who have not completed a primary vaccine series should be considered susceptible. When tetanus toxoid and TIG are given concurrently, separate syringes and separate sites should be used.

6. Recommendations for post-exposure prophylaxis in HIV-infected adults
• TIG is recommended in all HIV-positive persons following a possible exposure, regardless of CD4 count and according to the table given below (B, III)
Tetanus-prone wounds

- Wound or burns that require surgical intervention and when that treatment is delayed for more than 6 hours
- Wounds or burns that show any of the following characteristics: a significant degree of devitalised 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

7. Auditable outcomes

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

References


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1. Background

1.1 Tick-borne encephalitis virus
Tick-borne encephalitis, or TBE, is an infection caused by the tick-borne encephalitis virus (TBEV), a member of the flaviridae. Two closely related subtypes exist, Western (TBEV) and Eastern (Russian Spring-Summer Encephalitis virus, RSSEV), which cause similar diseases.

1.2 Clinical features
The typical course of TBE is biphasic. The first stage is characterised 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 subtype runs a similar course but carries a 20% risk of mortality. There is no specific drug therapy.

1.3 Epidemiology
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 North 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 and Slovak Republics, 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.

1.4 Transmission
The infection is transmitted to humans by the bite of an infected tick or, less commonly, by ingestion of unpasteurised milk from infected animals, mainly goats. Person-to-person transmission has not been reported.

1.5 Incubation period
7-14 days (range 2-28 days).

1.6 Risk groups
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 and tourists who camp, hunt and undertake field-work in rural, forested areas.

1.7 TBE in HIV-infected persons
It is not known whether the natural history of TBE is modified by HIV infection.

2. Pre-exposure prophylaxis: TBE Vaccine

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

2.2 Route of administration
The vaccine is given by intramuscular (or deep subcutaneous injection in case of bleeding disorders), preferably in the deltoid.

2.3 Schedule of administration in the general healthy population

<table>
<thead>
<tr>
<th>Schedule</th>
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<tbody>
<tr>
<td><strong>Standard schedule</strong></td>
<td>2 doses 3-12 weeks apart</td>
<td>2 doses 4-12 weeks apart</td>
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<tr>
<td>Primary course</td>
<td>9-12 months later</td>
<td>9-12 months later</td>
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<tr>
<td>Third dose</td>
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<td></td>
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<tr>
<td>2 doses 14 days apart</td>
<td>N/A</td>
<td>3 doses on days 0, 7 and 21</td>
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<tr>
<td>Fourth dose</td>
<td>9-12 months later</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Rapid schedule</strong></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Primary course</td>
<td>3 doses on days 0, 7 and 21</td>
<td></td>
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<tr>
<td>Third dose</td>
<td>N/A</td>
<td>12-18 months later</td>
</tr>
<tr>
<td>Fourth dose</td>
<td>N/A</td>
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</table>

The standard vaccination schedule consists of 2 doses given over 3-12 or 4-12 weeks, followed by a third dose 9-12 months later. The rapid schedules have shown similar efficacy in healthy individuals and are practical for travellers. Whether the rapid vaccination schedule is effective in HIV-infected persons is unknown.

2.4 Vaccine efficacy in healthy individuals
The vaccine protects against infection with both TBEV and RSSEV. In immunocompetent adults, the rate of seroconversion after 3 doses is 85%-100%.

2.5 Vaccine efficacy in HIV-positive individuals
Only two published studies have investigated the immunogenicity of TBE vaccination in HIV-infected patients [2, 3]. These studies suggest that the vaccine is less efficacious in HIV-infected individuals than in HIV-negative persons, particularly at CD4 counts <500 cells/mm³. Although a four-dose vaccination schedule given at 0, 1, 2, and 9-12 months may improve responses in HIV-infected persons [3], evidence in support of this strategy remains limited [2].
2.6 Duration of protection
Among healthy individuals, prospective follow-up studies have demonstrated that only 52% of vaccine recipients maintain protective levels of antibodies 42 months after the third immunization. For those at risk boosting is recommended every 3 years. The duration of protection in HIV-infected persons is unknown, but may be reduced compared with HIV-negative individuals. There is no evidence to guide a change in boosting recommendations.

2.7 Adverse events
TBE vaccine is safe and well tolerated in HIV-infected individuals with CD4 count >200 cells/mm$^3$ [1-4]. 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-Barre 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.

2.8 Contraindications
- A history of previous severe adverse reaction or allergy to the vaccine or its components.
- Severe allergy to eggs.
- Persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated.
- There is no evidence that the vaccine causes damage to the foetus. However, it should not be given during pregnancy unless there is a specific indication. With the vaccine produced from inactivated virus the theoretical risk to the developing foetus is expected to be low.
- The vaccine may cause deterioration of some autoimmune conditions and a risk assessment should be made before administering the vaccine in these conditions.

2.9 Pre- and post-vaccination testing
A neutralising antibody response above 126 Vienna Units/ml is considered to be protective. Post-vaccination testing is not routinely recommended in healthy individuals, but may be considered in some immunocompromised persons (see below). Information on TBE serological testing is available at the Special Pathogens Reference Unit (SPRU), Health Protection Agency, Centre for Emergency Preparedness and Response, Porton Down, Salisbury, Wiltshire, SP4 0JG. Tel: +44 (0) 1980 612224. Email: special.pathogens@hpa.org.uk
Website: http://www.hpa.org.uk/srmd/other_ref_labs/spru.htm
3. Recommendation for pre-exposure prophylaxis in HIV-infected adults

- Immunisation 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).
- Either the standard or the rapid vaccination schedule may be considered for HIV-infected persons with CD4 counts >400 cells/mm$^3$ (see section 2.3) (C, IV).
- In HIV-infected individuals with a CD4 count <400 cells/mm$^3$, serological testing may be considered one 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 at 9-12 months after the first dose (C, IV). In the absence of serological testing, a 4-dose vaccination schedule (0, 1, 2 and 9-12 months) should be adopted to improve response rates (C, IV).
- Due to the possibility of reduced responses to vaccination, the importance of protective clothing and insect repellent use should be emphasised.
- A booster is recommended every three years for those at continued risk (C, IV).

4. Post-exposure prophylaxis

None available

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)

References

1. Dr. Herwig Kollaritsch, Infectious Disease Unit, Medical University of Vienna, Vienna, Austria (personal communication)
4. Dr. Maria Peallabauer, Baxter Vaccine AG, Vienna, Austria (personal communication).

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- **Conflict of interest:** None
1. Background

1.1 *Salmonella typhi*
Typhoid fever is caused by the Gram negative bacillus *Salmonella*, serogroup *typhi* (*S. Typhi*). Nearly 2000 salmonella serotypes are recognised, but most cause non-invasive infections of the gastrointestinal tract. *S. typhi*, *S. paratyphi A*, *B*, and *C* and occasionally other salmonella species may cause invasive infections. Vaccination is only available against *S. typhi*.

1.2 Clinical features
Disease severity varies, but typhoid fever can be life-threatening. The onset is insidious with fever, headache, abdominal pain, malaise, body aches and anorexia. About half of patients have constipation and 30% have diarrhoea. Fever can reach 39-40°C by the end of the first week and can be associated with relative bradycardia in adults. By the second week a rash may appear on the abdomen (“rose-spots”). Confusion, delirium, intestinal haemorrhage and perforation, and multi-organ involvement may occur. Untreated, the illness may last for 3 to 4 weeks, with a 12-30% risk of mortality. Complications are generally observed during the third or fourth week. Antibiotic therapy leads to resolution of symptoms within 2 to 3 days, and deaths is rare in treated persons. Relapses may occur despite antibiotic therapy. About 10% of patients with typhoid fever excrete the organism for three 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.

1.3 Epidemiology
Typhoid fever is common in the developing world. Between 12 and 33 million cases of occur each year worldwide, with the highest incidence in Asia (especially the Indian subcontinent), Africa, and Latin America, and 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 being reported. Multidrug-resistant strains of *S. typhi* have become common in the Indian subcontinent and the Middle East.

1.4 Transmission
*S. 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.

1.5 Incubation period
5-21 days.
1.6 Risk groups
Travellers to Asia, Africa, and Latin America who have prolonged exposure to potentially contaminated food and drink are especially at risk of infection [1,2]. In these regions, the attack rate for travellers has been estimated at 10 per 100,000 travellers.

1.7 Typhoid fever in HIV-infected persons
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 [3,4]. Disease manifestations among HIV-infected persons without severe immunocompromise 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 [5]. Patients with AIDS may present with more severe disease, including fulminant diarrhoea or colitis [3].

2. Pre-exposure prophylaxis: Typhoid vaccine

2.1 Vaccine composition
Three typhoid vaccines are available: a) the parental ViCPS vaccine, containing purified Vi (“virulence”) capsule polysaccharide and the only one available in the UK; b) the oral Ty21a vaccine*, containing live attenuated Salmonella typhi Ty21a; and c) a whole-cell inactivated vaccine. A combined hepatitis A and ViCPS vaccine is also available.

2.2 Route of administration
The ViCPS vaccine is given by intramuscular injection (or subcutaneous injection in persons with bleeding disorders), preferably in the deltoid.

2.3 Schedule of administration in the general healthy population
The ViCPS vaccine is given as a single dose. It can be given simultaneously with other vaccines relevant for international travellers such as the vaccines against yellow fever and hepatitis A [1,2].

2.4 Vaccine efficacy in healthy individuals
Typhoid vaccines are approximately 50-80% effective. The vaccine's protection can be overwhelmed by large inocula of S. typhi [1,2]. One dose of the ViCPS vaccine induces antibodies in 93% of healthy adults [6,7]. Two trials in disease-endemic areas have demonstrated the clinical efficacy of ViCPS in preventing laboratory-confirmed typhoid fever. In Nepal, a study of persons aged 5-44 years showed 74% (95% confidence interval 49% to 87%) vaccine efficacy over a follow-up period of 20 months [8]. In South Africa, a trial in children aged 5-16 years showed 55% (95% confidence interval 30% to 71%) efficacy over a 3 year follow-up period. The efficacy in years 1, 2, and 3, was 61%, 52%, and 50%, respectively [9,10]. The vaccine should be given at least 2 weeks before travel to ensure adequate protection [1,2].

*Contraindicated in HIV-infected persons
2.5 Vaccine efficacy in HIV-positive persons
Although the ViCPS vaccine is safe for HIV-infected persons, the induction of protective antibodies is directly correlated to the levels of CD4 positive T-cells. The antibody response in patients with CD4 count <200 cells/mm$^3$ is significantly lower compared with patients with higher CD4 counts and healthy controls [17].

2.6 Duration of protection
In a metanalysis, the ViCPS vaccine provided protection for two 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. The duration of protection may be reduced in HIV-infected persons.

2.7 Adverse events
Injection site reactions, including swelling, redness, or pain have been reported in up to 7% of ViCPS recipients and usually resolve within 48 hours. 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 and no significant increase in plasma HIV RNA load has been observed after vaccination [17].

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.

2.8 Contraindications
- A history of previous severe adverse reaction or allergy to the ViCPS vaccine or its components.
- Persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated.
- The ViCPS vaccine should not be used in pregnancy unless there is a significant risk of infection.
- Persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated.
- 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.

2.9 Pre- and post-vaccination testing
Not recommended.

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*Contraindicated in HIV-infected persons
3. Recommendation for pre-exposure prophylaxis in HIV-infected adults:

- **Although not required for international travel, vaccination with the ViCPS vaccine is recommended in all HIV-infected persons who are due to travel 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. 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.

- Persons who will have intimate exposure (e.g., household contact) to a documented *S. typhi* carrier should also be offered vaccination (C, IV).

- The vaccine is also recommended for laboratory workers exposed to *S. typhi* (C, IV).

- A booster is recommended every 3 years in those who remain at risk. This interval might be considered to be reduced to 2 years, if the CD4 count is <200 (C, IV)

4. Passive immunoprophylaxis

None available

5. Post-exposure prophylaxis

Not recommended

6. Auditable outcomes

Number of at risk individuals who are vaccinated (Target 75%)

References


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- **Conflict of interest:** None

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- **Author’s affiliation:** Dept of Virology, Royal Free Hospital, Pond Street, London NW3 2QG
- **Conflict of interest:** None
1. Background

1.1 Mycobacterium tuberculosis
The *Mycobacterium tuberculosis* complex includes *M. tuberculosis*, *M. bovis* and *M. africanum*. *M. tuberculosis* is a rod-shaped bacterium.

1.2 Clinical features
Depending on host factors, infection with *M. tuberculosis* may be cleared, remain latent or progress to active tuberculosis (TB) 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 reactivate. The life-time risk of reactivation is 5-15% for immunocompetent adults. The majority of reactivations occur within 2 years of primary infection.

1.3 Epidemiology
Active tuberculosis affects as many as 10 million people per annum worldwide with deaths in 3–5 million. In the UK cases fell progressively until the mid-1980s but started to rise again in the early 1990s [1,2]. Cases have increased by 25% in the last 10 years. Around 7000 cases are now reported each year in England and Wales, predominantly in high risk groups. The main stay 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 [3]. Vaccination contributes to the prevention and control of TB in limited situations.

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

1.5 Incubation period
Weeks to years.

1.6 Risk groups
In the UK a large number of reported TB 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 born [2]. 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. The risk of disease is greatest in persons with immunodeficiency, especially HIV infection. Other key risk factors for disease are diabetes mellitus, renal failure, immunosuppressive therapy, acquisition of
latent infection in infancy or early childhood, and therapy with TNF-alpha antagonists [3].

1.7 TB in HIV-infected persons
The risk for active TB disease is high among HIV-infected persons and worldwide TB is the leading cause of death among HIV infected people. HIV also suppresses responses to the tuberculin test.

2. Pre-exposure prophylaxis: BCG vaccine

2.1 Vaccine composition
The Bacille Calmette-Guerin (BCG) vaccine* is a live attenuated vaccine containing a strain of *M. bovis* isolated in 1908 from a cow, which was subcultured 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, which differ in their production techniques and characteristics. BCG Vaccine Statens Serum Institut (SSI)* is the only available licensed vaccine in the UK [2].

2.2 Route of administration
The BCG vaccine* is administrated intradermally in the later aspect of the left upper arm, using a multi-puncture device [2]

2.3 Schedule of administration in the general population
The BCG vaccine* is given as a single dose following the continuing decline in active TB rates in indigenous population the BCG school programme was stopped. BCG vaccine* is now recommended for selected high-risk infants and children, and for previously unvaccinated tuberculin-negative close contacts of those with active respiratory TB [2]. 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 one month or longer [1, 2].

2.4 Vaccine efficacy in healthy individuals
Studies of BCG vaccine* are difficult to interpret as 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. In a

* Contraindicated in HIV-infected persons
meta-analysis of 10 randomised studies and 8 case-control studies there was 86% protection (95% confidence interval: 65% to 95%) against meningitis and military disease in children in the randomised studies and 75% protective efficacy (95% confidence interval: 61% to 84%) in the case-control studies [3]. The rates of protective efficacy against pulmonary TB differed considerably between studies, precluding an estimation of the overall effect. A second meta-analysis reviewed the results of 14 clinical trials and 12 case-control studies and showed an overall protective effect of 51% in the clinical trials (95% confidence interval: 30% to 66%) and 50% in the case-control studies (95% confidence interval: 36% to 61%) [4]. 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 with persons vaccinated at older ages. There are virtually no data on vaccine efficacy in persons aged 35 years and over.

2.5 Vaccine efficacy in HIV-positive persons

The protective efficacy of BCG vaccine* in children and adults who are infected with HIV has not been determined.

2.6. Duration of protection

Protection is thought to last for at least 10-15 years but data are limited. Repeat vaccination is not recommended.

2.7 Adverse events

The BCG vaccine* often causes local adverse effects, but serious or long-term complications are rare in healthy individuals. Possible factors affecting the rate of adverse reactions include the BCG dose, vaccine strain, method of vaccine administration and host-related factors. Within 10–14 days 90-95% of vaccine recipients develop an erythematous papule at the injection site, with induration and tenderness. vaccination. 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 less than 1cm [2].

Severe injection site reactions (e.g., discharging ulcers, abscesses and keloid scarring) 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) [2].

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 [5-12]. Disseminated BCG disease after vaccination has occurred in at least one child and one adult who were infected with HIV. These complications can occur several years after

* Contraindicated in HIV-infected persons
BCG vaccination. Studies in Zaire, Haiti and Congo however did not demonstrate an association between HIV seropositivity and adverse responses to BCG vaccination [13, 14].

2.8 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 over-riding reason to offer vaccination. No further immunisation should be given in the arm used for BCG immunisation for at least three months because of the risk of regional lymphadenitis. Other contraindications include: past history of TB, induration of 6mm 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 BGC vaccination is indicated in infants born to HIV-positive mothers it should only be administered after two appropriately timed negative post-natal PCR-based HIV tests.

2.9 Pre- and post-vaccination testing
The international standard for determining immunity to TB is the Mantoux tuberculin skin test using purified protein derivative (PPD) [1]. The current reagent is an unlicensed product. The Mantoux requires special skills to administer and read properly. An assay based on the detection of interferon-gamma may supersede the Mantoux as it appears to be more sensitive and specific.

3. Recommendation for pre-exposure prophylaxis in HIV-infected adults
- Until the risk-benefits of BCG vaccination in HIV-infected adults is established, the vaccine is absolutely contraindicated in all HIV-positive persons regardless of CD4 count and clinical status (C, IV).
- BCG is also contraindicated in persons suspected to be HIV positive, regardless of clinical status (C, IV).

4. Passive immunoprophylaxis
None available

5. Post-exposure prophylaxis
None available

6. Auditable outcomes
Record history of childhood or other BCG vaccination in newly diagnosed HIV-infected persons (Target 95%)
References

- **Author 1:** Anton Pozniak
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- **Conflict of interest** None
1. Background

1.1 Varicella zoster virus
Varicella zoster virus (VZV) is a member of the herpes virus family. Primary infection typically causes varicella (chicken pox). Subsequent reactivation of latent infection causes zoster (shingles).

1.2 Clinical features
Varicella is characterised by a generalised vesicular-papular rash. Whereas immunocompetent children usually have benign and self-limiting disease, adults are more likely to develop severe varicella leading to hospitalisation and risk of mortality. Complications of varicella include severe or disseminated 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. Rarely, infection in pregnancy leads to foetal injury (congenital varicella syndrome).

Zoster is a self-limiting, painful, localised 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 (post-herpetic neuralgia). Cutaneous dissemination or visceral involvement may occur in individuals with compromised immunity.

1.3 Epidemiology
In temperate climates, primary infection with VZV most commonly occurs during childhood. At least 90% of adults in England & Wales are VZV IgG seropositive [1], confirming prior infection. In tropical and subtropical climates, the mean age of primary VZV infection may be delayed. As a result a significant proportion of individuals raised in those regions remain VZV IgG seronegative and susceptible to primary infection in adulthood [2]. Zoster is common in immunocompetent individuals with an overall rate of 373 per 100,000 population years [3].

1.4 Transmission
Varicella is highly infectious and can be transmitted by the respiratory route up to 48 hours 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.

1.5 Incubation period
10-21 days.

1.6 Risk groups
Patients with cellular immunodeficiency who acquire varicella are at risk for severe or disseminated cutaneous disease, secondary bacterial infection of skin lesions, and visceral
involvement. In addition these patients are at risk of severe disease and complications following the development of zoster. Pregnant women who develop varicella in the third trimester are at increased risk of pneumonia.

1.7 VZV in HIV-infected persons
Patients with HIV infection are at risk for developing severe illness from either varicella or zoster. Varicella is relatively uncommon among HIV-infected adults from temperate countries, reflecting the high rate of VZV acquisition in childhood. Conversely, a significant proportion of HIV-infected adults from tropical countries may be susceptible to the infection [4]. Varicella is frequently complicated in HIV-infected adults. Progressive primary varicella, a syndrome with persistent new lesion formation and visceral dissemination, may be life-threatening. In the pre-HAART era, approximately 25% of in-patients with varicella developed severe complications including haemorrhagic rash, pneumonitis and fulminant infection with disseminated intravascular coagulation [4].

HIV-infected persons have a higher frequency of zoster. Although most have an uncomplicated clinical course, patients are prone to complications including multidermatomal, disseminated and chronic atypical skin rashes [5]. Acute retinal necrosis and neurological syndromes including encephalitis, myelitis, and meningitis frequently occur in the absence of rash [5]. Zoster continues to be common in the era of HAART and has been recognised as a manifestation of immune reconstitution disease [6].

2. Pre-exposure prophylaxis: Varicella Vaccine

2.1 Vaccine composition
The VZV vaccine contains live attenuated VZV propagated in human diploid cells. Two vaccines are available currently based on the OKA strain (Varilrix®, Glaxo SmithKline) and the OKA/Merck strain (Varivax ®Aventis Pasteur MSD). The vaccine can establish latent infection in some vaccinees and reactivate to cause zoster. However, this occurs less often than with wild-type virus.

2.2 Route of administration
The vaccine is administered by subcutaneous injection, preferably in the deltoid.

2.3 Schedule of administration in the general healthy population
In the UK the varicella vaccine is currently recommended for:
- Healthcare workers with a negative or uncertain history of chickenpox or zoster, who test VZV IgG seronegative, and who do not have contraindications to vaccination.
- Healthy susceptible contacts of immunocompromised patients.

Individuals ≥13 years should receive 2 vaccine doses.
Varilrix: the two doses are given 8 weeks apart, with a minimum interval of 6 weeks.
Varivax: the two doses are given 4-8 weeks apart.
If the interval exceeds 8 weeks, the second dose should be given as soon as possible

2.4 Vaccine efficacy in healthy individuals
In immunocompetent adults, 2 doses of varicella vaccine give 75% protection against any disease and >95% protection against severe disease [7]. Vaccination of VZV IgG seropositive immunocompetent adults with the VZV vaccine to boost natural immunity has recently been shown to halve the incidence of herpes zoster and to reduce the frequency of postherpetic neuralgia by two thirds [8].

2.5 Vaccine efficacy in HIV-positive persons
The immunogenicity of the VZV vaccine has been demonstrated in VZV IgG seronegative children with asymptomatic or mildly symptomatic HIV infection and preserved immunity [9]. After 2 doses, 60% seroconverted for VZV IgG and 83% showed T-cell proliferative responses. Consideration of vaccination has been recommended for this patient group [5, 10]. There are limited data on the efficacy of vaccination among HIV-infected adults. Among VZV IgG seropositive persons with nadir CD4 counts >400 cells/mm$^3$ and stable on antiretroviral therapy for at least 3 months, the vaccine can boost VZV-specific cellular immune responses [11]. Less robust responses have been observed in patients with a nadir CD4 count <200 cells/mm$^3$ restored to >400 cells/mm$^3$ with HAART [12].

2.6 Duration of protection and boosting requirements
Among HIV-negative adults, waning immunity over time is manifest by mild breakthrough infections with wild-type virus. Vaccinated healthcare workers followed for up to 8 years after vaccination have an attack rate of 10% [13]. Vaccinated individuals may require additional booster doses later in life. This is currently under investigation.

2.7 Adverse events
Up to 10% of immunocompetent adults develop a vaccine-associated rash, localised at the site of injection or generalised, within one month of immunisation [14, 15]. Severe but non-fatal varicella vaccine-associated disease has been reported in some children with undiagnosed immunodeficiency [16]. Overall however the vaccine is regarded as safe in children with asymptomatic or minimally symptomatic HIV infection and an age-specific CD4 count ≥15% [17]. In VZV IgG seropositive HIV-infected adults with CD4 >400 cells/mm$^3$ while on HAART no excess adverse events have been reported following VZV vaccination [11, 12]. In addition no significant effects on HIV plasma RNA load have been observed [9]. The vaccine strain is sensitive to antiviral therapy with acyclovir.

Transmission of vaccine virus from vaccinees has been documented only rarely and only from individuals with vaccine-associated rashes. Vaccination is not contraindicated 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 Health Protection Agency Varicella Reference Service [http://www.clinical-virology.org/pages/vzrl/vzrl_summary.html](http://www.clinical-virology.org/pages/vzrl/vzrl_summary.html)
2.8 **Contraindication**
- A history of previous severe adverse reaction or allergy to the vaccine or its components.
- Persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated.
- The vaccine is contraindicated in pregnancy and during breastfeeding.
- The vaccine is contraindicated in patients with cellular immunodeficiency.

2.9 **Pre- and post-vaccination testing**
There are no agreed standards for VZV serological tests. A history of varicella is usually a reliable indicator of VZV IgG seropositive status. VZV IgG can be tested to identify susceptible persons among those who do not report a history of varicella. Serological testing for evidence of seroconversion is not routinely recommended in healthy individuals but may be indicated in selected cases.

3. **Recommendation for vaccine use in HIV-infected adults**
There are very limited data on the efficacy and safety of the VZV vaccine in HIV-infected adults and the VZV vaccine is not generally recommended in immunocompromised persons [7, 10]. Because HIV-infected persons are at increased risk for morbidity from varicella and zoster compared with healthy persons, vaccination of susceptible HIV-infected adults who have no evidence of significant immunocompromise may be a useful strategy to prevent both varicella and zoster in this population [5].

- HIV-infected adults with a negative or uncertain history of varicella should be tested for VZV IgG and seronegative individuals should be considered for vaccination according to the following guidelines:
  - **After weighing potential risks and benefits, varicella vaccination is recommended for VZV IgG seronegative asymptomatic HIV-infected adults who have preserved immune function (CD4 count >400 cells/mm$^3$)** (C, IV)
  - **Vaccination may also be considered for VZV IgG seronegative asymptomatic HIV-infected patients with CD4 counts <400 cell/mm$^3$ but >200 cell/mm$^3$ while on stable HAART** (C, IV).
  - Two vaccine doses are recommended. A three month interval is recommended between doses (C, IV).
  - Patients who develop a post-vaccine rash or other adverse effects should receive prompt medical evaluation and antiviral therapy for VZV (C, IV). The Health Protection Agency can be contacted for further advice on individual cases [http://www.clinical-virology.org/pages/vzrl/vzrl_summary.html](http://www.clinical-virology.org/pages/vzrl/vzrl_summary.html)
  - Following vaccination, HIV-infected individuals should undergo serological testing to demonstrate VZV IgG seroconversion (C, IV). Testing should be performed 4-6 weeks following the second vaccine dose.
  - It is hoped that immunization of VZV seropositive HIV-infected patients will decrease the incidence of shingles and studies to determine this are under way [5]. No specific recommendations can be made at present.
4. Recommendation for vaccine use in close contacts of HIV-infected adults
The VZV vaccine is recommended for VZV-seronegative close contacts of HIV-infected adults [7, 10] (C, IV). The risk of transmission of the vaccine virus is significantly less than the risk of transmission of varicella.

5. Post-exposure prophylaxis: VZV Vaccine
After VZV vaccination, cellular immunity develops within 4 days and has been shown to confer protection shortly after contact. Varivax, but not Varilrix, is licensed for post-exposure prophylaxis in susceptible individuals exposed to VZV if administered within 3 days of exposure. The manufacturers of Varivax quote limited data supporting its use up to 5 days post-exposure [18]. Available evidence supports post-exposure prophylaxis with the VZV vaccine in healthy HIV-negative individuals [19]. Protection is <100% however, with mild cases of infectious chickenpox occurring especially after household exposure.


6.1 VZV Immunoglobulin
Varicella-zoster immunoglobulin (VZIG), made from pooled plasma of non-UK donors with suitably high titres of VZV antibody, is indicated for VZV IgG seronegative 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/mm^4 [7]. It should be administered within 10 days and, ideally, within 7 days of exposure [7].

6.2 Route of administration
VZIG is given by intramuscular injection. Where intramuscular injection is contraindicated in individuals with bleeding disorders, intravenous immunoglobulin (0.2g per kg body weight) may be given instead.

6.3 Schedule of administration
VZIG should be given as soon as possible after a contact, preferably within 7 days and up to 10 days.

6.4 Duration of protection
The duration of protection is 3 weeks. In the event of a second exposure after 3 weeks, repeat administration of VZIG prophylaxis is recommended [7].

6.5 Adverse events
Rare anaphylactic reactions have occurred in individuals with hypogammaglobulinanaemia or prior blood transfusion reactions.

6.6 Pre-immunisation testing
VZV IgG seronegative status should ideally be confirmed prior to VZIG administration. In vulnerable cases with no history of chickenpox and where VZV IgG cannot be tested within 7 days of exposure, VZIG should be administered without testing [7].

6.7 VZIG efficacy in immunocompromised persons
VZV antibody negative, HIV-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 [20]. By comparison with the expected 90% case rate in unprotected household contacts, VZIG has a protective efficacy of 40% [20]. There is no published evidence of VZIG efficacy in HIV-infected patients.

7. Post-exposure prophylaxis: Antiviral therapy
Limited data indicated that varicella in healthy children may be prevented, or attenuated, by administration of acyclovir starting between 7 and 10 days after exposure, for a total of 7 days [21, 22]. The equivalent dose of acyclovir in adults is 800mg four times daily. There are no published controlled trials comparing acyclovir prophylaxis directly with VZIG.

8. Recommendation for post-exposure prophylaxis in HIV-infected persons
Following a significant exposure of an HIV-infected patient to varicella or zoster, their VZV IgG status should be ascertained if possible. Seronegative patients should be considered for post-exposure prophylaxis and closely monitored for symptoms of varicella. Prophylaxis should be tailored to the patient’s clinical status and the following approach is recommended:

Symptomatic HIV infection and/or CD4 <400 cell/mm³ (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. Prophylaxis should not be delayed beyond 7 days pending availability of test results. The patient should be observed closely for signs or symptoms of varicella for 28 days following exposure.
- Antiviral post-exposure chemoprophylaxis with oral acyclovir (800 mg four times daily or equivalent) may be considered if VZIG is not available, or given in conjunction with VZIG in profoundly immunocompromised patients (C, IV).

Asymptomatic HIV infection and CD4> 400 cell/mm³ with or without HAART (C, IV).
- Consider post-exposure prophylaxis with Varivax (Varilrix is not licensed for prophylaxis) within three days of exposure. Varicella vaccinees should be warned to report post-vaccine rashes or other symptoms and be evaluated promptly for antiviral therapy. The second dose should normally be scheduled after three months with subsequent serological testing to confirm VZV IgG seroconversion. There are currently no data supporting this recommendation and the risk of vaccine-related adverse events must be balanced against the risk of severe complications resulting from natural infection in these patients.
9. Auditable outcomes
Determine the VZV susceptibility status of HIV-infected patients with a significant exposure to varicella or zoster (target 100%)
Offer VZV screening and subsequent varicella vaccination to VZV IgG seronegative household contacts of severely immunocompromised HIV-patients. Target 80%.

References

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1. **Background**

**1.1 Yellow fever virus**
The yellow fever virus (YFV) is a flavivirus transmitted by mosquitoes.

**1.2 Clinical features**
The severity of infection with YFV 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 [1]. There is no antiviral or other effective therapy.

**1.3 Epidemiology**
YFV is prevalent in tropical and subtropical regions of Africa and South America, where it is endemic and intermittently epidemic. 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 savanna zones of West and Central Africa. In West Africa, the most dangerous time of year is during the late rainy and early dry seasons (July-October). Outbreaks occur occasionally in urban locations and villages in Africa; to a lesser extent, infections also occur in jungle regions. 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 ten years from the tenth day after primary vaccination and immediately after revaccination.

**1.4 Transmission**
The YFV is transmitted from monkey to monkey, monkey to man, and man to man predominantly by *Aedes aegypti* mosquitoes.

**1.5 Incubation period**
3-6 days.

**1.6 Risk groups**
Travellers to endemic areas are at risk of infection. The risk of acquiring yellow fever is determined by immunisation status, location of travel, season, duration of exposure, occupational and recreational activities while travelling, and the local rate of YFV transmission at the time. The risk for illness in travellers to yellow fever-endemic areas has been estimated to be 0.4-4.3 cases per million travellers [2].

**1.7 Yellow fever in HIV-infected persons**
There are no data to indicate whether the natural history of yellow fever is modified by HIV infection.

2. **Pre-exposure prophylaxis: YFV vaccine**
2.1 Vaccine composition
In the UK two products (Stamaril – Aventis-Pasteur; Arilvax – Evans Medical Ltd.) are available, each consisting of a live attenuated preparation of the 17D strain of YFV grown in chick embryos.

2.2 Route of administration
The YFV is given by subcutaneous injection, preferably in the deltoid.

2.3 Schedule of administration in the general healthy population
The YFV is given as a single dose. Vaccination can only be given at designated centres competent in Yellow fever vaccination in the UK. Other live-virus vaccines may be given concurrently; alternatively 4 weeks should be allowed to elapse between sequential vaccinations.

2.4 Vaccine efficacy in healthy individuals
A single dose of the YFV vaccine has a protective efficacy of 90% after 10 days and 99% after 30 days [1].

2.5 Vaccine efficacy in HIV-positive persons
Data regarding seroconversion rates after YFV vaccination among HIV-infected persons are limited. Although development of neutralising antibodies may be reduced [3, 4], seroconversion rates of approximately 70% have been observed in HIV-infected adults with CD4 counts >200/mm$^3$ [5]. Good responses have also been reported in asymptomatic HIV-infected adults with CD4 ranging between 240 and 1300 cells/mm$^3$, most of whom where on HAART at the time of vaccination [6].

2.6 Duration of protection
The YFV vaccine provides protection 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. The duration of protection in HIV infected persons is unknown, but may be reduced compared with HIV-negative persons.

2.7 Adverse events
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 immunisation. More serious adverse events are very rare and less common in those who have had previous immunisation. These are principally hypersensitivity or anaphylaxis (1 in 130,000 to 250,000), neurotropic disease (1 in 250,000 to 8 million) and the recently-recognised viscerotropic disease (1 in 40,000 to 1,200,000) [7, 8]. The latter two complications have been increasingly recognised in older recipients, with a combined incidence of 1 in 25,000 and 1 in 13,000 for those in the 60-69 and ≥70 years age groups respectively [7]. The viscerotropic disease is characterised by multi-organ involvement and 50% risk of mortality. Clinically and pathologically resembles naturally acquired yellow fever. A history of thymic dysfunction may be a risk factor.
These data have led to many older travellers being advised not to undergo vaccination, rather receive a certificate of exemption, when absolute risks of infection are low. Additional surveillance to better monitor and quantify yellow fever vaccine-specific adverse outcomes should be established. Studies are being conducted to clarify the cause and risk factors for these rare adverse events associated with the yellow fever 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/mm$^3$, either in early HIV infection or following HAART [3-6, 9]. In addition no appreciable effect of vaccination on CD4 count or HIV viral loads has been observed [6]. There has been only one published case of post-vaccine fatal encephalomyelitis, in a Thai man with asymptomatic infection and a CD4 count of 108 cells/mm$^3$, after receiving this vaccine [10].

2.8 Contraindication
There are three groups of adult people who should not receive the vaccine unless the risk of yellow fever disease exceeds the small risk associated with the vaccine. These people should obtain either a waiver letter prior to travel or delay travel to an area with active yellow fever transmission:
1. Those with severe adverse reaction or allergy to the vaccine or its components, or with egg allergy.
2. Pregnant and breastfeeding women due to a theoretical risk to the foetus.
3. Persons with immunodeficiency due to disease or treatment

Current UK Department of Health recommendations for yellow fever vaccination exclude those with HIV infection at all stages [11], whilst the American Advisory Committee on Immunisation Practices (ACIP), recommends it may be given to those travelling to high risk areas with a CD4 count >200 cells/mm$^3$ [9].

Persons with acute moderate or severe febrile illness usually should not be vaccinated until their symptoms have abated.

2.9 Pre- and post-vaccination testing
Data on seroconversion rates among asymptomatic HIV-infected persons are limited. Measurement of the neutralizing antibody response to vaccination could be considered before travel, but this test is of limited availability.

3. Recommendation for pre-exposure prophylaxis in HIV-infected adults
- Asymptomatic HIV-infected persons with CD4 count >200 cells/mm$^3$ who are due to travel to countries in which there is a risk of exposure to yellow fever infection should be offered the choice of vaccination, after appropriate counselling of the risks (B, III).
- Physicians should be careful to administer yellow fever vaccine only to persons truly at risk for exposure to yellow fever. If international travel requirements and not true
exposure risk are the only reasons to vaccinate an asymptomatic HIV-infected person, a waiver letter should be given.

- Vaccination should be undertaken at least two weeks before travel and vaccine recipients should be monitored closely after vaccination (C, IV).
- Those travelling to low risk areas who require a certificate of vaccination should be given a certificate of exemption (C, IV)
- HIV-infected adults with CD4 count <200 cells/mm$^3$ 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. If travel to high risk areas is absolutely necessary, they should receive a certificate of exemption. Travellers should be warned that vaccination waiver documents may not be accepted by some countries and that if this waiver is rejected, the option of deportation might be preferable to yellow fever vaccination at the destination (C, IV).
- Due to the possibility of reduced responses to vaccination in HIV-infected persons, the importance of precautions against mosquito bites should be emphasised in all patients.
- A booster is indicated after 10 years for those at risk, provided the CD4 count is >200 cells/mm$^3$ (C, IV).

4. Post-exposure prophylaxis
None available.

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%).

References

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