Immunisation against infectious disease / prepared by the Joint Committee on Vaccination and Immunisation for the Secretary of State for Social Services, the Secretary of State for Scotland and the Secretary of State for Wales.

Immunisation against Infectious Disease

1984

IMMUNISATION AGAINST INFECTIOUS DISEASE

Prepared by the Joint Committee on Vaccination and Immunisation for the Secretary of State for Social Services, the Secretary of State for Scotland and the Secretary of State for Wales

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IMMUNISATION AGAINST INFECTIOUS DISEASE

1 INTRODUCTION

1.1 General

1.1.1 This Memorandum describes the vaccines, immunoglobulins and antisera which are in routine use in this country. Suggested schemes for immunisation in childhood are included and advice is given on storage of the various agents, techniques of vaccination and the need to keep accurate records of immunisations carried out. Vaccines which may be of value in special circumstances but which are not regularly used are also mentioned. While the recommendations are generally applicable, it is emphasised that it is for the individual doctor to decide on the type, dosage and timing of the vaccine given.

1.1.2 Immunity can be induced either actively or passively against a variety of bacterial and viral agents:

a. Passive immunity results from injecting preparations of human immunoglobulin or antisera; the latter are usually derived from immunised horses. Such immunity is temporary and lasts only for months until the foreign sera have been eliminated from the body. Nevertheless the protection afforded is rapid. By contrast most active immunisation procedures provide protection for many years.

b. Active immunity can be induced by using either inactivated or live and suitably attenuated agents. Sometimes an attenuated strain of the living organism causing the disease may be used, or it may be possible to use a related organism. Live vaccines of this nature include oral poliomyelitis vaccine (OPV), measles vaccine, rubella vaccine and BCG vaccine. Other bacterial and viral vaccines make use of organisms which have been inactivated during manufacture, such as whooping cough, typhoid and inactivated poliomyelitis (IPV) vaccines. On the other hand influenza and pneumococcal vaccines may contain only specifically identified immunising components of the micro-organisms. Tetanus and diphtheria vaccines rely for their immunising effect on the presence of toxoid, which is the bacterial toxin detoxicated by treatment with formaldehyde.

1.1.3 Most vaccines, apart from BCG, produce their protective effect by stimulating the production of specific protective antibodies which are detectable by laboratory tests. An important additional effect of oral poliomyelitis vaccine is the establishment of local immunity in the intestine. The protection afforded by BCG vaccine is attributed to a cell-mediated immunity mechanism.

1.1.4 A first injection of vaccine in a subject who has had no prior experience of the antigen produces a slow antibody or antitoxin response. This is predominantly IgM antibody and is usually referred to as the "primary response". It may take two injections to produce such a response. Depending on the potency of the product and the time interval, further injections will lead to an accelerated response in which the antibody or antitoxin titre rises to a higher level and very much more quickly. This type of response, characterised by IgG antibody, is referred to as a "secondary response". Following a full basic course of vaccination as shown in the subsequent schedules, the antibody or antitoxin levels may remain high for months or years, but even if the level of antibody falls off the immune mechanism remains sensitised so that a further dose of vaccine will elicit a secondary response and reinforce immunity.

1.1.5 Some vaccines contain adjuvants; substances which enhance the antibody response. Examples are aluminium phosphate and aluminium hydroxide, which are used in diphtheria and tetanus vaccines. Triple (diphtheria, tetanus, pertussis) vaccine may also contain an aluminium salt as an adjuvant; it is considered that the aluminium compound delays the absorption of the immunising agent in the body, thereby increasing its efficacy.

1.2 Precautions to be observed before carrying out immunisation procedures.

1.2.1 Administration of all vaccines or other immunological products carries some risk of a reaction, although serious reactions are very rare. Details of possible reactions, and of specific contra-indications, are given in the sections dealing with individual vaccines. It is stressed that these recommendations are only for the general guidance of doctors and nurses; they are not comprehensive. It is advisable also to take note of the advice in the package insert provided by the manufacturer, which accompanies each vaccine container and may provide further information on substances in the vaccines to which the individual may show an allergy.

1.2.2 In most circumstances immunisation, particularly of young children, is an elective procedure; it is therefore important to ascertain that no contra-indication exists before any vaccination is carried out. It is recognised that adverse reactions occur more frequently following immunisation of individuals suffering from conditions which may be associated with a vaccine hazard, and immunisation of these individuals should be avoided. In general:

a. It is advisable to postpone immunisation if the patient is suffering from any acute febrile illness, particularly respiratory, until fully recovered. (Minor infections without fever or systemic upset are not regarded as a contra-indication).

b. Live vaccine should not be administered to pregnant women, particularly early in pregnancy, because of possible harm to the fetus. However, where there is a significant risk of exposure to such serious conditions as poliomyelitis or yellow fever the importance of vaccination may outweigh the possible risk to the fetus.

c. Live vaccines should not be administered to patients receiving corticosteroid or immunosuppressive treatment, including general radiation, or to those suffering from malignant conditions such as lymphoma, leukaemia, Hodgkin's disease or other tumours of the reticulo-endothelial system, or where the normal immunological mechanism may be impaired as, for example, in hypogammaglobulinaemia.

d. Apart from these general considerations there are contra-indications to individual vaccines and these are listed in the relevant sections.

If it is necessary to administer more than one live virus vaccine at the same time, they may be given simultaneously at different sites (unless a combined preparation is used). If not given simultaneously, administration of live virus vaccines should be separated by an interval of at least 3 weeks. It is also recommended that a 3 week interval should be allowed between the administration of live virus vaccines and the giving of BCG.

1.2.3 A sterile syringe and adrenaline injection BP (1 in 1,000 adrenaline) should be ready for use in case the need arises for emergency treatment of an allergic reaction.

Initial dose 0.5ml for adults. For young children the initial dose is:-

0.05ml for infants aged 3 - 5 months
0.075ml for infants aged 6 - 11 months
0.1ml for infants aged 1 year

Adrenaline BP should be given by intramuscular injection.

1.3 Surveillance and reporting of adverse reactions

1.3.1 Before being released for general use, vaccines are extensively tested in animals and human volunteers to show their safety and efficacy, and subsequently in field trials in human subjects. It is nevertheless important to maintain careful surveillance. This depends on early, complete and accurate reporting of adverse reactions and it is very important that any abnormal clinical event following the administration of a vaccine, whether or not considered to be due to the vaccine, *should be reported on a yellow card without delay to the Committee on Safety of Medicines.*

1.3.2 Organisations such as the Public Health Laboratory Service carry out a programme of epidemiological and serological surveillance in order to provide a continual assessment of vaccines.

1.4 Sequence and timing of injection

1.4.1 During recent years a number of changes have taken place both in the vaccines recommended for administration and in their method of use. There is still room for discussion on detail, but there is fairly general agreement on certain important aspects. These include the desirability of a basic course of immunisation with diphtheria, tetanus and pertussis vaccine during the first year of life with oral poliomyelitis vaccine being given at the same time. This is followed by measles vaccination during the second year of life and reinforcement of immunisation with diphtheria, tetanus and oral polio vaccine at school entry. On this general framework many variations have been built.

1.4.2 In the past there has been some variation in practice in regard to the age at which the basic course of vaccination begins. At one time it was thought that there might be some advantage in delaying commencement until a child had reached the age of 6 months, but it is now considered that in order to ensure a high

acceptance rate and protection against whooping cough in early life, vaccination should begin at the age of 3 months. In this connection it should be noted that the majority of deaths and much of the severe illness associated with whooping cough occurs in infants.

1.5 Intervals between doses

1.5.1 Mention has already been made of the difference in the responses to the first and subsequent vaccine doses. To obtain the best secondary response the second dose must be given at the appropriate interval after the first dose. This calls for an interval between the first and second injections rather longer than the 4-weeks' interval which has been customary in the past and the interval now recommended is 6-8 weeks. In order to obtain a durable immunity the interval between the second and third injections should be even longer, and an interval of 4-6 months is recommended. Precise adherence to these intervals is not however essential for infants whose basic course of DTP or poliovirus vaccine has been interrupted; a single additional dose later in infancy (or 2 doses where only the first dose of the basic course had been given) is considered adequate to establish immunity, regardless of the time elapsing between the initial and subsequent doses.

1.5.2 Every effort should be made to make arrangements for the vaccination of infants, preferably at the recommended intervals, and appropriate arrangements are usually made at the first domiciliary visit by a health visitor. The majority of those areas which are linked to a computer system, which calls for a child to be present for immunisation at the appropriate time, have achieved striking improvements in the acceptance rates.

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2 IMMUNISATION TECHNIQUES

2.1 General

2.1.1 Before administering any immunological product, particularly a vaccine, attention should be paid to the following points:

a. Leaflets supplied with products should be read carefully. They are prepared by the manufacturer in consultation with the licensing authority and contain the essential basic information regarding the indications, contraindications and methods of administration.

b. Check the identity of the vaccine or other immunological product and make sure that the vaccine or serum required is the one contained in the ampoule or vial.

c. Note carefully the date of expiry of the product.

d. Record the batch number.

e. Check that the storage conditions have been satisfactory (see paragraph 6).

f. A sterile syringe and adrenaline injection BP (1 in 1,000 adrenaline) should be ready for use, in case the need arises for emergency treatment of an allergic reaction.

Initial dose 0.5ml for adults. For young children the intial dose is:-

0.05ml for infants aged 3 - 5 months
0.075ml for infants aged 6 - 11 months
0.1ml for infants aged 1 year

Adrenaline BP should be given by intramuscular injection.

2.2 Reconstitution of vaccines

2.2.1 Many modern vaccines are freeze-dried and so have to be reconstituted with a diluent, which is normally provided by the manufacturer. It is essential that the appropriate diluent is used.

2.2.2 When reconstituting measles or rubella vaccines, note carefully whether the diluent is sucked into the vial when the needle is inserted through the cap, without any pressure being exerted; this will indicate whether the vacuum is still present. Finally, before inoculation, check that the colour of the product is as stated by the manufacturer in the package insert. In all cases the diluent should be added slowly. If the diluent is injected with too great pressure, it will result in frothing with an adverse effect on the vaccine. A sterile 1ml syringe with a 21G needle should be used for reconstituting the vaccine, with a small gauge needle (see table - page no. x) for the actual injection.

2.3 Cleaning of skin

2.3.1 With most vaccines, the skin should be swabbed with a suitable bactericide or by commercially prepared "mediswabs". The alcohol must be allowed to evaporate before the vaccine or other product is administered, since alcohol can inactivate live vaccine preparations.

2.4 Route of administration

2.4.1 Depending on the nature of the product, the route of administration may be as follows:

a. *By mouth.* Oral polio vaccine should only be administered by the oral route and *never* by injection. Three drops of vaccine should be added to a spoon containing syrup or placed on a lump of sugar or on a disposable plastic spoon and given immediately to the patient, and the spoon placed in disinfectant. Batches of sugar lumps should not be prepared with OPV before immunisation and kept at room temperature as this may decrease the potency of the vaccine.

b. *Multiple pressure or scratch technique.* Smallpox vaccine, now only necessary for a few people in exceptional occupations, is usually administered by multiple pressure with 10 pressures for primary vaccination and 30 for re-vaccination or by single scratch 0.5cm long. Details can be found in the Memorandum on Vaccination against Smallpox issued by the Department in 1974.

c. *Subcutaneous and intramuscular.*

i. It is usually recommended that the intramuscular or deep subcutaneous routes for administration be used for all vaccines except BCG and, sometimes, typhoid, cholera and rabies vaccines, which may be given by the intradermal route. The policy on the preferred site for deep intramuscular injections may be a matter for local clinical agreement.

ii. Careful attention should be paid to the recommended route as shown in the manufacturer's leaflet. Dose volumes and needle guage are shown in the table.

d. *Intradermal inoculations.* BCG vaccine is usually given in this way and, in special circumstances, typhoid, cholera and rabies vaccines. The recommended doses and needles are shown in the table, page no. x. When giving an intradermal injection the operator should stretch the skin between the thumb and forefinger of one hand and with the other slowly insert the needle, with the bevel upwards, for about 2mm into the superficial layers of the dermis almost parallel with the surface. The needle should be short with a short bevel which can usually be seen faintly through the epidermis during insertion. A raised, blanched, bleb showing the tips of the hair follicles is a sign that the injection has been made correctly and its diameter gives a useful indication of the amount which has been injected. If this is not felt and it is suspected that the needle is too deep, it should be removed and re-inserted before more vaccine is given. A bleb of 7mm diameter is approximately equivalent to 0.1ml.

e. *Suitable sites of intradermal injections.*

i. For intradermal typhoid, cholera and rabies vaccines the site of injection is behind the posterior border of the distal portion of the deltoid muscle.

ii. For BCG the site of injection is usually in the area over the insertion of the left deltoid muscle.

iii. For sensitivity tests, intradermal injections are usually given in the middle of the front of the forearm. *This site should not be used for injecting vaccines.*

2.5 Dosage

2.5.1 In all cases the dose is indicated in the leaflet.

2.6 Storage

2.6.1 It is imperative that all concerned with immunisation adhere to the manufacturer's recommendations on storage before the product is used. This is usually at refrigerator temperature between 2-8°C (36-46°F); it is important not to store vaccine for reconstitution at temperatures below 0°C as freezing could cause deterioration of the product or breakage of the diluent container. It is even more important to ensure that the reconstituted vaccine is used within the recommended period of reconstitution. This varies from 1 to 4 hours according to the manufacturer's recommendations. Multi-dose vials MUST NOT be used after a vaccination session. The use of single-dose containers is preferred, but where this is not possible any multi-dose vials should be used at once after opening.

TABLE

Vaccine	*Route of administration*	*Usual dose*	*Recommended needle*
OPV	Oral	3 drops	Nil
IPV	Deep subcutaneous or intramuscular	0.5 ml	23G
DPT) DT)	Deep subcutaneous or intramuscular	0.5 ml	23G
Measles) Rubella) Mumps)	Deep subcutaneous or intramuscular	0.5 ml	23G

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Vaccine	*Route of administration*	*Usual dose*	*Recommended needle*
Typhoid	) Deep subcutaneous or	0.5 ml	23G
Cholera	) intramuscular intradermal	0.1 ml	25G
BCG	Intradermal	0.1 ml †	25G
Rabies	(Deep subcutaneous or	1.0 ml	23G
	(intramuscular intradermal	0.1 ml	25G
Anthrax	Deep subcutaneous or intramuscular	0.5 ml	23G
Hepatitis B	Deep subcutaneous or intramuscular	1.0 ml	23G

† For infants the dose should be reduced to 0.05ml

Immunoglobulin	*Route of administration*	*Usual dose*	*Recommended needle*
Normal or Hyper-immune	Deep subcutaneous or intramuscular	250 mg in 1.7 - 2.5 ml**	23G

**Dose required expressed as mg/kg body weight.

Smallpox Multiple pressure or scratch 0.05 ml - 21G or Wyeth needle (where recommended).

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3. WHOOPING COUGH

3.1 Introduction

3.1.1 Whooping cough is a highly communicable bacterial disease, caused by *Bordetella pertussis,* which primarily affects the trachea and bronchi. The initial catarrhal stage has an insidious onset with an irritating cough which gradually becomes paroxysmal, usually within 1-2 weeks, and often lasts for 2-3 months. Spread is by droplet infection and the incubation period is 7-10 days. It is communicable from 7 days after exposure to 3 weeks after the onset of typical paroxysms. Numerous inapparent and atypical cases occur. Whooping cough may be complicated by lung damage such as collapse or bronchopneumonia, and by cerebral anoxia which may cause brain damage. The severity of whooping cough is dependent on age, with the majority of complicated cases and deaths occurring in infants, in particular in those under 6 months of age. As there is no transfer of passive immunity to whooping cough from the mother to the newborn infant, neonates are susceptible to whooping cough from birth.

3.1.2 In the early 1950's the average annual number of notifications of whooping cough was over 100,000, in 1957 whooping cough vaccination was recommended on a national scale and in the decade to 1967 the average annual number of notifications fell to less than 30,000 and in the decade to 1977 to under 10,000 a year.

3.1.3 The case fatality ratio dropped from over 10 per 1,000 cases notified in the early 1940's to about 1 : 1,000 cases in 1953 to 1956. It remained at that level for the next 20 years and then fell abruptly to 0.2 per 1,000 in 1976.

3.1.4 The fall-off in uptake of vaccination in 1974 caused major epidemics in the years 1977/79 and 1981/83.

3.1.5 The contribution of vaccination to these changes has been the subject of much discussion in recent years, particularly in view of uncertainty about the incidence of serious neurological side-effects to the vaccine. A number of studies has shown that a

full course of vaccine confers protection in over 80 per cent of the recipients and that the severity of the illness is less in those who do contract the illness despite immunisation. The dramatic rise in notifications during 1977-1978 following the equally sudden drop in vaccination rates during the preceding few years is now generally accepted as evidence of the effectiveness of the vaccine in the prevention of clinical cases. In the 1977/79 and the 1981/82 epidemics children under the age of five were badly affected by the disease; however in the more recent epidemic children in the age group five to nine years have also shown higher attack rates. This point emphasises the need to vaccinate children against whooping cough before they enter school; unless this is done a further epidemic may occur in 1985 irrespective of an increase in vaccine uptake among children in the first year of life. The benefits conferred by vaccination greatly outweigh the very small risk of serious neurological reactions which may arise in relation to pertussis vaccine.

3.2 Whooping cough vaccine

3.2.1 Whooping cough vaccine is a suspension of killed *B. pertussis* organisms with an estimated potency of not less than 4 i.u. in each 0.5 ml of vaccine. Organisms bearing the three principal pertussis agglutinogens are included. The vaccine is available as a monovalent vaccine or combined with diphtheria and tetanus vaccines either in plain form (DTPer/Vac) or adsorbed with aluminium hydroxide (DTPer/Vac/Ads). It should be stored between 2-8°C, but not frozen. The vaccine should be administered by deep subcutaneous or intramuscular injection.

3.3 Recommendations

3.3.1 Whooping cough vaccine as a component of the basic course of immunisation (DTPer/Vac/Ads) is recommended for infants from 3 months of age, unless contra-indications exist (see under contra-indications).

3.3.2 A basic course consists of three doses given with an interval of 6-8 weeks between the first and second doses and 4-6 months between the second and third doses. If whooping cough is prevalent it is desirable to protect a child at the earliest age possible, therefore an alternative course of triple vaccine with one month's interval between the first and second and second and third doses commencing at the age of 3 months should be

considered. However such a course should be followed at 12-18 months of age by a dose of DT/Vac/Ads vaccine since the intervals of one month are considered not to give adequate basic immunity against diphtheria and tetanus. If the basic course is interrupted, it should be resumed, observing the appropriate time intervals for those doses which remain. There is no need to re-start the course or repeat earlier doses. Adsorbed triple vaccine is preferred to the plain vaccine for use in the basic course as it is more immunogenic and causes fewer local reactions.

3.3.3 Monovalent pertussis vaccine is available for use when the pertussis component has been omitted from earlier vaccinations and there is a need to complete the basic course of immunisation. Children who have received a full course of vaccination against diphtheria and tetanus should be given 3 doses of single pertussis vaccine at monthly intervals. Where the basic course against diphtheria and tetanus is incomplete, triple vaccine may be used to begin or complete the course against whooping cough. Children between their fourth and sixth birthdays whose primary course of diphtheria and tetanus vaccine has been completed more than 3 years ago and who are due for their pre-school booster dose, should be given triple vaccine (DTPer/Vac/Ads) as their first dose of the course of immunisation against whooping cough. The second and third doses of whooping cough vaccine should then be given in the form of single pertussis vaccine. Pertussis vaccine should not normally be given after the 6th birthday and there is no need to give reinforcing doses after the basic course of three injections.

3.3.4 Infants for whom whooping cough vaccine is contra-indicated, or infants whose parents do not wish their child to have whooping cough vaccine, should be offered a basic course of DT/Vac/Ads.

3.4 Side-effects and adverse reactions

3.4.1 a. Transient fever, headache, malaise, somnolence and local reactions at the site of injection may be encountered. A small painless nodule may form at the injection site but usually disappears without sequelae.

b. Neurological reactions may occasionally arise following pertussis vaccination, and these may range in severity from an isolated febrile convulsion or an episode

of excessive screaming to a severe encephalopathy resulting in permanent brain damage or death. No wholly reliable estimate of the incidence of such complications can be made as events of this type occur, often from unknown causes, in both immunised and unimmunised children and their frequency is greatest in the first year of life. Only a small proportion of these events are the result of pertussis immunisation and it is impossible to identify those cases which are related to immunisation by any clinical or laboratory test. The best estimate of the magnitude of this problem puts the risk of an apparently normal infant suffering a severe neurological reaction following pertussis vaccination at about 1 in 100,000 injections. Not all such reactions lead to permanent brain damage. The risk of vaccination resulting in permanent brain damage is estimated as being about 1 in 300,000 injections, or a 1 in 100,000 chance of permanent brain damage for a child given a full course of 3 injections.

3.4.2 *It is extremely important that the contra-indications to whooping cough vaccination should be observed.*

3.4.3 It is most important that adverse reactions to whooping cough vaccine be reported to the Committee on Safety of Medicines using the yellow card system.

3.5 **Contra-indications to whooping cough vaccination**

3.5.1 a. It is advisable to postpone vaccination if the child is suffering from any acute febrile illness, particularly respiratory, until fully recovered. (Minor infections without fever or systemic upset are not regarded as a contra-indication).

b. Vaccination should not be carried out in children who have:

i. a history of any severe local or general reaction (including a neurological reaction) to a preceding dose;

ii. a history of cerebral irritation or damage in the neonatal period, or who have suffered from fits or convulsions.

c. There are certain groups of children in whom whooping cough vaccination is not absolutely contra-indicated but who require special consideration as to its advisability. These groups are:

i. children whose parents or siblings have a history of idiopathic epilepsy;

ii. children with developmental delay thought to be due to a neurological defect;

iii. children with neurological disease.

3.5.2 For these groups the risk of vaccination may be higher than in normal children but the effects of whooping cough may be more severe, so that the benefits of vaccination would also be greater. The balance of risk and benefit should be assessed with special care in each individual case.

3.5.3 A personal or family history of allergy has in the past been regarded as a contra-indication to vaccination but there is now a substantial body of medical opinion which no longer considers this to be so. Doctors should, however, use their own discretion in the individual case.

3.5.4 Even when pertussis vaccine is contra-indicated an infant should still be considered for immunisation against diphtheria and tetanus.

3.6 Management of outbreaks

3.6.1 Vaccination has little to offer in the management of a localised outbreak of whooping cough as it is too late for active immunisation to protect susceptible contacts. Previously immunised children will be less likely to contract the disease than those who are unimmunised and in addition they will be less severely affected than unimmunised children if they develop whooping cough.

3.7 Supplies

3.7.1 a. Adsorbed diphtheria-tetanus pertussis vaccine (DTPer/ Vac/Ads): one 0.5ml dose consists of a mixture in isotonic saline of diphtheria toxoid and tetanus toxoid adsorbed on to aluminium hydroxide gel together with

not more than 20,000 million *B. pertussis* bearing the 3 principal agglutinogens. The potency of the diphtheria component is not less than 30 i.u., that of the tetanus component not less than 40 i.u., and that of the pertussis component not less than an estimated 4 i.u. Thiomersal is added as a preservative to a final concentration of 0.01 per cent. Manufactured by **Duncan, Flockhart and Co, Ltd, and by *Wellcome Foundation Ltd.

b. Diphtheria-tetanus pertussis vaccine (DTPer/Vac): one 0.5ml dose consists of a mixture in isotonic saline of diphtheria toxoid, tetanus toxoid and not more than 20,000 million *B. pertussis* bearing the three principal agglutinogens. The diphtheria component consists of not less than 25 Lf of toxoid, the tetanus component of 5 Lf of toxoid, and the pertussis component has an estimated potency of not less than 4 i.u. Thiomersal is added as a preservative to a final concentration of 0.01 per cent. Manufactured by *Wellcome Foundation Ltd.

c. Monovalent pertussis vaccine; One 0.5ml dose contains not more than 20,000 million *B. pertussis* bearing the three principal agglutinogens. Thiomersal is added as a preservative to a final concentration of 0.01 per cent. Manufactured by the *Wellcome Foundation Ltd.

** **Duncan Flockhart & Co Ltd., Tel No. 01-739 3451**

* **Wellcome Foundation Ltd., Tel No. Crewe (0270) 583151**

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4. DIPHTHERIA

4.1 Introduction

4.1.1 Diphtheria is now a rare acute infectious disease affecting the upper respiratory tract and occasionally the skin. It is characterised by an inflammatory exudate which forms a greyish membrane and may cause respiratory obstruction. The incubation period is from 2 to 5 days and whilst it is communicable for up to 4 weeks, carriers may continue to shed organisms for longer. A toxin is produced by the diphtheria bacilli which has a special affinity for, and affects the cellular activity of, heart muscle, nervous and adrenal tissue. Spread of the bacilli is from person to person or by contact with articles soiled by infected persons.

4.1.2 The most effective protection against the disease is by active immunisation with diphtheria toxoid, now referred to as diphtheria vaccine. The introduction of immunisation against diphtheria on a national scale in 1940 has resulted in a dramatic fall in the number of notified cases and deaths from this disease. In 1940, 46,281 cases with 2,480 deaths were notified, whereas in 1957, 37 cases with 6 deaths were notified and in the last 5 years there have been 14 cases notified and only 1 death. The disease and the organism have been virtually eliminated and there is now no possibility of natural immunisation from sub-clinical infection. Consequently, both children and a substantial proportion of adults will be susceptible to infection if they have not been immunised. A high vaccine acceptance rate must be maintained in order to protect children against the possibility of a resurgence of the disease.

4.2 Diphtheria Vaccine

4.2.1 Diphtheria vaccine is prepared from a cell free preparation of the toxin treated with formaldehyde. Each 0.5ml dose of either single or combined standard vaccine contains 24 Lf (Lf - flocculating units) of toxoid. A low dose diphtheria vaccine for adults will become available in 1984 (containing 1.5 Lf) for the immunisation of individuals over the age of 10 years. These products should be stored between 2 - 8°C. The vaccine should be injected deep subcutaneously or intramuscularly. It protects by stimulating the production of antitoxin and thus immunity to the effects of the toxin. Used alone both types of vaccine are weak antigens and need to be adsorbed onto an adjuvant (aluminium phosphate or hydroxide) in order to stimulate an adequate immune response.

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Standard vaccine is usually given as combined vaccine either with tetanus vaccine or with both tetanus and pertussis vaccines. The basic course of three doses correctly administered should confer immunity in almost 100 per cent of susceptible persons.

4.2.2 Standard diphtheria vaccine combined with tetanus and pertussis vaccines as triple antigen adsorbed onto an adjuvant is recommended for use in the basic course of immunisation in infancy (DTPer/Vac/Ads), because it stimulates a better immune response and fewer reactions than non-adsorbed vaccine (DTPer/Vac). When it is decided to omit the pertussis component, adsorbed diphtheria and tetanus vaccine (DT/Vac/Ads) is available for establishing immunity in the basic course.

4.3 Recommendations

4.3.1 Vaccination against diphtheria is recommended:

a. *For primary immunisation of children under 10 years of age*

Diphtheria vaccine as a component of triple vaccine or combined with tetanus vaccine is recommended for infants from 3 months of age. A basic course consists of 3 doses, each containing 25 Lf diphtheria toxoid given with an interval of 6-8 weeks between first and second doses and 4-6 months between the second and third dose. If the basic course is interrupted, it should be resumed observing the appropriate time intervals for those doses which remain. There is no need to restart the course or repeat earlier doses. A reinforcing dose of diphtheria and tetanus vaccine combined is recommended for children at school entry and preferably after an interval of at least 3 years from the last dose of the basic course.

b. *Immunisation of persons 10 years of age or over*

Unless an individual is likely to be exposed to diphtheria, adult type, low dose (1.5 Lf) vaccine should be used and administered by deep subcutaneous or intramuscular injection without prior Schick testing. For reinforcement a single dose of 0.5 ml is required. For primary immunisation : 3 doses of 0.5 ml separated by intervals of one month.

4.4 Use of the Schick test

4.4.1 *The Schick test is recommended to test the immunity of those individuals likely to be exposed to diphtheria in the course of their work.*

For this group it is advisable to ensure that immunity to diphtheria exists, which cannot reliably be done by examination of immunisation records. Such employees could safely be given a booster dose or full course of diphtheria vaccine for adults, but for those who had failed to receive childhood immunisation and were wrongly recorded as immunised, a single dose of adult diphtheria vaccine would fail to produce immunity. In cases of doubt, therefore, especially if exposure is a real possibility, it is advisable to test that immunity has actually been induced. This could be done by antitoxin titration of Schick testing performed not less then three months after completion of immunisation.

Note: In the past the Schick test has been recommended for:-

a. individuals who have been exposed to a case of diphtheria and in whom it is necessary to detect their need for immunisation. For individuals over the age of 10 years in whom a reaction to diphtheria vaccine may be troublesome, the availability of adult-type vaccine toxoid, makes the Schick test unnecessary and they could be given a booster dose or a full course of adult toxoid depending on whether or not they had been previously immunised. Children under the age of 10 years are not liable to experience severe reactions to diphtheria vaccine. For these children the booster dose of standard toxoid would suffice if they had been previously immunised, or for those not immunised, a complete course of ordinary toxoid. Unimmunised contacts should also receive a standard course of erythromycin prophylaxis.

b. children in residential schools where diphtheria immunisation is advised, it would be satisfactory to rely on immunisation records to decide whether a full course of toxoid or a booster dose was needed; the standard toxoid or adult vaccine should be used depending upon age.

4.5 Schick Test

4.5.1 An intradermal injection of 0.2 ml of Schick test toxin is given into the anterior surface of the left forearm and 0.2 ml of Schick test control (inactivated toxin) material into the corresponding position of the other forearm using separate syringes and needles. Readings should be made at 24-48 hours and 5-7 days. Comparison of the appearances of the two injection sites will reveal reactions attributable to immunity and to allergy. Four types of response may occur:-

a. **Schick negative** - No visible reaction on either arm. The subject is immune and need not be immunised or boosted.

b. **Schick positive** - An erythematous reaction develops at the site of the toxin injection, becoming evident 24-48 hours later and persisting for 7 days or more before gradually fading. The control shows no reaction. The subject is not immune and may require to be immunised or boosted.

c. **Negative-and-pseudo reaction** - Both injection sites show similar reactions after 48-72 hours, which fade within 5-6 days. The reactions are due to hypersensitivity to the components of the test materials. The subject need not be immunised or boosted.

d. **Positive-and-pseudo reaction** - (also called combined reaction). Both injection sites show reactions after 48-72 hours but the reaction in the arm given toxin is usually larger and more intense than that on the control arm. The control response fades considerably by the 5th-7th day leaving the positive effect clearly evident. Such combined reactors usually have a basal immunity to diphtheria and should not be immunised with a further full course of vaccine. Their immunity can successfully be boosted by means of a single dose of adult (1.5 Lf) vaccine.

4.6 Side effects and adverse reactions

4.6.1 Transient fever, headache, malaise and local injection site reactions may be encountered. A small painless nodule may form at the injection site but usually disappears without sequelae. Severe anaphylactic reactions are rare. Neurological reactions have been reported occasionally. Any severe reaction observed following vaccination with diphtheria vaccine should be reported to the Committee on Safety of Medicines, using the yellow card system.

4.7 Contra-indications

4.7.1 As with other immunising procedures, diphtheria immunisation is elective except when dealing with the control of a known case and it is important to ensure that no known contra-indication exists either to it or to other vaccines with which it is combined. It should not be given if the patient is suffering from acute febrile illness. 25 Lf vaccine should not be given to children over the age of 10 years or to adults without a preliminary Schick test with control to avoid severe reactions in persons already immune or those who are hypersensitive.

4.8 Diphtheria Antitoxin

4.8.1 This antitoxin is derived from horses and because of the presence of foreign protein its use may provoke a hypersensitivity reaction. It is rarely needed for prophylaxis in unimmunised contacts if prompt investigation, surveillance, antibiotic prophylaxis and the use of vaccine are provided. *In cases of suspected diphtheria, as the antitoxin is specific it should be given without the delay of awaiting bacteriological confirmation of the disease.* Tests with a trial dose to exclude hypersensitivity should first be carried out. The dosage will depend on the clinical condition of the patient and it may be given either intramuscularly or intravenously.

4.9 Supplies

4.9.1 Adsorbed diphtheria and tetanus vaccine (DT/Vac/Ads) consists of a mixture of diphtheria (25 Lf) and tetanus (5 Lf) toxoids adsorbed on to aluminium hydroxide in 0.5 mls of isotonic

buffer solution. Manufactured by the Wellcome Foundation Limited *Tel: Crewe (0270) 583151 and Duncan Flockhart & Co Ltd. **Tel: 01-739 3451.

4.9.2 Adsorbed diphtheria, tetanus and pertussis vaccine (DTPer/Vac/Ads) has the same composition as the above with the addition of killed whole *Bordetella pertussis.* Manufacturers as above.

4.9.3 Adsorbed diphtheria vaccine (Dip/Vac/Ads), consists of diphtheria toxoid (25 Lf) adsorbed on to hydrated aluminium phosphate. Manufactured by the Wellcome Foundation Ltd.* Tel: Crewe (0270) 583151.

4.9.4 Diphtheria, tetanus and pertussis vaccine (DTPer/Vac) and diphtheria and tetanus vaccine (DT/Vac/FT) have the same antigenic composition as the adsorbed vaccines noted above, (2) and (1), but contain no aluminium adjuvant. Manufactured by the Wellcome Foundation Ltd.* Tel: Crewe (0270) 583151.

4.9.5 Adsorbed Diptheria Vaccine for Adults (Dip/Vac/Ads for Adults) Swiss Serum & Vaccine Institute, Berne, and distributed in the UK by Regent Laboratories Limited, Cunard Road, London NW10 6PN. Telephone 01-965 3637.

4.9.6 Schick Test Toxin (Diluted) and Schick Test Control BP. Manufactured by Wellcome Foundation Ltd.* Tel: Crewe (0270) 583151.

4.9.7 Diphtheria antitoxin BP/Eur Ph. consists of boxes of 10 x 5 ml vials (2000 iu per ml) and individually packaged vials of 10 ml (2000 iu per ml). Manufactured by the Swiss Serum and Vaccine Institute, Berne, and distributed in the UK by Regent Laboratories Ltd. Cunard Road, London NW10 6PN (Tel: 01-965 3637).

* **Wellcome - Crewe (0270) 583151**

** **Duncan Flockhart 01-739 3451**

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IMMUNISATION AGAINST INFECTIOUS DISEASE

5. TETANUS

5.1 Introduction

5.1.1 Tetanus is an acute disease characterised by muscular rigidity with superimposed, painful contractions induced by the toxin of tetanus bacilli which grow anaerobically at the site of an injury. The incubation period is between 4 and 21 days, commonly about 10. Tetanus spores are present in soil and may be introduced into the body during injury, often a puncture wound but also with burns or trivial, unnoticed wounds. Tetanus neonatorum due to infection of the baby's umbilical stump is an important cause of death in many countries of Asia, Africa and South America. Tetanus is not spread from person to person and can affect people of all ages.

5.1.2 Active immunisation is the most effective method of preventing tetanus. Routine immunisation against tetanus was introduced as a national policy into the basic course of immunisation of infants in 1961. It was recognised that it was difficult to designate any group of people for whom immunisation against tetanus is particularly needed or any age at which it should be started as although people in certain occupations, such as agricultural workers, might be at special risk, those injured in road accidents or in their own gardens or children at play may also be infected. From 1960 - 1969, the incidence of tetanus in England and Wales was believed to be in the region of 200 - 300 cases a year with approximately 27 deaths each year in which tetanus was implicated. In 1970 the Joint Committee on Vaccination and Immunisation endorsed the recommendations made by an Advisory Group on Protection Against Tetanus, that universal active immunisation should be the ultimate goal. Other recommendations were that active immunity to tetanus should be initiated when treating wounds and firm arrangements made for giving further doses of toxoid which may be required to complete the basic course at the appropriate time either at the hospital, by the general practitioner or by the staff of the local health authority.

5.1.3 In the last decade, notifications of tetanus have fallen to around 20 cases a year with 22 deaths during the five year period 1974-78. The most significant decline in notifications has been in those aged under 20 years with no recorded cases in 1978 and 1979. Tetanus is thus progressively becoming an infection predominantly of older age groups who have not benefited from courses of primary immunisation.

5.2 Tetanus Vaccine

5.2.1 Tetanus vaccine is prepared from a cell free preparation of the toxin treated with formaldehyde. It protects by raising an immunity to the toxin. The vaccine should be stored at 2-8°C. It should be given by deep subcutaneous or intra-muscular injection. The vaccine may be in single or combined form. The single form can be in simple solution (Tet/Vac/FT) in which case a 0.5ml dose contains 20 Lf vaccine or when adsorbed on to aluminium hydroxide (Tet/Vac/Ads) 0.5ml contains 10 Lf. Tetanus vaccine can be combined with diphtheria vaccine (DT/Vac/FT : DT/Vac/Ads) or with diphtheria vaccine and pertussis vaccine (DTPer/Vac : DTPer/Vac/Ads); each dose in the combined preparations, which can be plain or adsorbed, contains 5 Lf vaccine. A basic course of adsorbed vaccine induces a very durable immunity in almost 100 per cent of susceptible persons.

5.3 Recommendations

5.3.1 Tetanus vaccine is recommended:-

a. *For primary immunisation of infants and children*

Tetanus vaccine combined with diphtheria and pertussis vaccine (DTPer/Vac/Ads) or combined with diphtheria vaccine alone (DT/Vac/Ads) is recommended for infants from 3 months of age. A basic course consists of 3 doses of adsorbed vaccine with intervals of 6-8 weeks between the first and second dose and 4-6 months between the second and third doses. A reinforcing dose of diphtheria and tetanus vaccine combined is recommended, preferably with an interval of at least 3 years from the last dose of the basic course, for children at school entry. A further reinforcing dose of tetanus vaccine alone is recommended for those aged 15-19 years or on leaving school.

b. *Adults*

Tetanus vaccine is recommended particularly for selected groups such as patients with wounds attending accident departments of hospitals, factory workers, farm workers, gardeners and members of emergency services. The basic course consists of 3 doses with intervals of 6-8 weeks between the first and second dose and 4-6 months between the second and third doses. A reinforcing dose 5 years after this course and another 5 to 15 years later should provide a satisfactory degree of protection. The adsorbed vaccine is antigenically more potent and its use is indicated when establishing the basic immunity and when antitoxin is given following an injury. Plain vaccine may be used if local reactions have arisen to previous doses. Every effort should be made to encourage the patient given tetanus vaccine following an injury to complete the basic course of active immunisation.

5.3.2 Once a basic course of tetanus vaccine has been given, a satisfactory degree of protection against tetanus may be provided by a single reinforcing dose of vaccine in the event of an injury which is considered might give rise to tetanus. These reinforcing doses should not be given at too frequent intervals as they may provoke hypersensitivity reactions. Tetanus vaccine should not routinely be given to any patient who has received a booster dose in the preceding 5 years, unless the wound is regarded as carrying an unusually high risk of tetanus, and even then vaccine is not necessary if a booster has been given during the preceding year. The treatment of an individual will always be decided by the doctor in clinical charge who will consider the need for human anti-tetanus immunoglobulin in the passive protection of the individual case.

5.4 Side effects and adverse reactions

5.4.1 Local injection site reactions may arise and persist for several days. They may also arise some 10 days after the injection. General reactions, which are uncommon, are headache, lethargy, malaise, myalgia and pyrexia. Acute anaphylactic reactions and urticaria may occasionally occur, and rarely peripheral neuropathy. Persistent nodules at the injection site may arise if the injection is not given deeply enough. Severe reactions observed following immunisation with tetanus vaccine should be reported to the Committee on Safety of Medicines using the yellow card system.

5.5 Contra-indications

5.5.1 Reinforcing doses of tetanus vaccine at frequent intervals may provoke hypersensitivity reactions and should be avoided. As with other immunising procedures, routine immunisation against tetanus is elective and it is important to ensure that no known contra-indications exist either to it or to other vaccines with which it is combined. It should not be given if the patient is suffering from acute febrile illness unless the patient has a tetanus-prone wound. In the management of tetanus-prone wounds, combined active and passive immunisation may be needed; for this purpose, *adsorbed* tetanus vaccine should be administered in a different limb to the one receiving the tetanus immunoglobulin. Tetanus vaccine in simple solution may not raise a satisfactory level of immunity when given simultaneously with tetanus immunoglobulin.

5.6 Human Tetanus Immunoglobulin

5.6.1 The Joint Committee on Vaccination and Immunisation has endorsed the following advice from the Advisory Group on Protection Against Tetanus for the management of tetanus-prone wounds.

5.6.2 Whatever the patient's immune state, a thorough surgical toilet of the wound is regarded as essential and on no account must be omitted. The use of antibiotics for preventing any infection is a matter for clinical judgement, but for the specific prevention of tetanus, antitetanus immunoglobulin should be regarded as more effective. Immunoglobulin need rarely be used to protect patients already possessing an established basic immunity against tetanus, because in such individuals, adequate protection can be achieved by giving a single injection of tetanus vaccine, if the patient had not received one during the previous year. Human tetanus immunoglobulin should be considered in any patient not known to have been actively immunised and whose wound belongs to one or more of the following categories:

a. Any wound or burn sustained more than six hours before surgical treatment was given.

b. Any wound or burn at any interval after injury that shows one or more of the following characteristics:-

i. presence to a significant degree of devitalised tissue

ii. puncture-type of wound

iii. direct contact with soil or material likely to harbour tetanus organisms

iv. clinical evidence of sepsis.

5.6.3 For wounds not in the above categories, such as trivial clean cuts, immunoglobulin should not normally be given.

5.6.4 In inadequately immunised patients an adsorbed preparation of tetanus vaccine should be given at the same time into another limb, and arrangements made for the basic course of active immunisation to be completed. If a first or second dose is given at a hospital the course should be completed. This could be done either at the hospital or by the family doctor.

5.6.5 Patients with impaired immune responses may not respond to vaccine and may therefore require immunoglobulin whenever they suffer a wound of the types noted above.

5.6.6 These recommendations should be regarded as general guidance for the assistance of the doctor who must himself decide on the treatment of his own patient.

5.7 Supplies

5.7.1 Adsorbed diphtheria and tetanus vaccine (DT/Vac/Ads) consists of a mixture of diphtheria (25 Lf) and tetanus (5 Lf) toxoids adsorbed onto aluminium hydroxide in 0.5ml of isotonic buffer solution. Manufactured by the *Wellcome Foundation Limited and **Duncan,Flockhart and Co. Ltd.

5.7.2 Adsorbed diphtheria, tetanus and pertussis vaccine (DTPer/ VAC/Ads) has the same composition as the above with the addition of killed whole *Bordetella pertussis.* Manufacturers as above.

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5.7.3 Tetanus vaccine (Tet/Vac/Ads) contains detoxified toxin (10 Lf) adsorbed onto aluminium hydroxide. Manufactured by **Duncan, Flockhart and Co. Ltd. and the *Wellcome Foundation Ltd.

5.7.4 Diphtheria, tetanus and pertussis vaccine (DTPer/Vac) and diphtheria and tetanus vaccine (DT/Vac/FT) have the same antigen composition as the adsorbed vaccines noted above, (2) and (1), but contain no aluminium adjuvant. Manufactured by the *Wellcome Foundation Limited.

5.7.5 Human Tetanus Immunoglobulin (HTIG) is now generally available free-of-charge through Regional Transfusion Centres which will supply it to hospitals direct. It is prepared by the Blood Products Laboratory, Elstree, from blood donations collected by the National Blood Transfusion Service. The immunoglobulin is dispensed by hospital pharmacies in single dose containers of 250 i.u. in approximately 2.5ml. If local arrangements permit, general practitioners may obtain HTIG through this scheme. **Blood Products Lab. Elstree Tel: 01-953 6191.**

5.7.6 "Humotet" is the commercial equivalent of HTIG and contains 250 i.u. in 1ml. Manufactured by the *Wellcome Foundation Ltd.

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6. POLIOMYELITIS

6.1 Introduction

6.1.1 Poliomyelitis is an acute illness following invasion of the gastro-intestinal tract by poliovirus of which there are three types, types I, II and III. The infection may be clinically inapparent or range in severity from a non-paralytic fever, to aseptic meningitis or paralysis. Symptoms include, headache, gastrointestinal disturbance, malaise and stiffness of the neck and back, with or without paralysis. The incidence of inapparent infection usually exceeds clinical cases by about one hundred to one thousand fold. Poliomyelitis remains endemic in many developing countries and epidemics occur from time to time. In countries which have an established, large scale immunisation programme the disease occurs as sporadic cases or in outbreaks amongst unvaccinated individuals. Transmission is almost entirely from person-to-person through contact with the faeces or pharyngeal secretions of an infected person.

6.1.2 The incubation period ranges from 3 to 21 days, though commonly 7 to 12 days. Cases are most infectious from 7 to 10 days before and after the onset of symptoms. However, virus may persist in the faeces for 3 to 6 weeks or longer.

6.1.3 Inactivated poliomyelitis vaccine (Salk) was introduced by the Ministry of Health in 1956 for routine vaccination, and was replaced by attenuated live oral vaccine (Sabin) in 1962. Since their introduction, notifications of paralytic poliomyelitis have dropped from nearly 4,000 in 1955 to 257 in 1960 and to only a total of 35 cases during the 5 years - 1974-1978. This included 25 cases during 1976 and 1977, in which infection occurred with wild virus in unvaccinated persons. This demonstrates the continuing need to maintain high levels of vaccination uptake.

6.2 Poliomyelitis vaccine

6.2.1 Two types of poliomyelitis virus vaccines are available; oral poliovaccine (OPV) and inactivated poliovaccine (IPV). Oral poliovaccine (OPV) contains strains of living attenuated polio-viruses of type I, II and III. After issue from deep-freeze storage by the manufacturer, it should be kept refrigerated at 0-4°C. The

expiry date should be checked before use. Apart from the ease of administration, an advantage of the OPV over IPV is that the attenuated viruses become established in the intestine and produce both antibody formation in the blood and the gut epithelium thus providing local resistance to subsequent infection with wild poliomyelitis viruses. This has the effect of reducing the number of symptomless excreters of wild poliomyelitis virus in the community. OPV also interferes with simultaneous infection by wild polioviruses and is thus of particular value in the control of epidemics. Whilst many recipients are protected after a single dose, a full basic course of three vaccinations will produce long-lasting immunity to all 3 poliovirus types in more than 95 per cent of susceptible persons. Oral vaccine is issued in 10 dose containers. The vaccine stored unopened at 0-4°C is stable but once the containers are opened, the vaccine may lose its potency. For this reason any vaccine remaining in the containers at the end of an immunisation session should be discarded. To conserve supplies of vaccines, immunisation sessions should be arranged as far as possible to avoid undue wastage.

6.2.2 Inactivated poliovaccine (IPV) contains polioviruses of all three antigenic types, inactivated by formaldehyde. It is administered by deep subcutaneous or intramuscular injection. When used as recommended, IPV produces a serum antibody response to all 3 polioviruses in well over 90 per cent of recipients.

6.3 Recommendations

6.3.1 *Primary immunisation of children*

Oral poliovaccine is recommended for infants from 3 months of age. A basic course consists of 3 separate doses with intervals of 6-8 weeks between the first and second dose and 4-6 months between the second and third doses. For convenience these may be given simultaneously with vaccinations against diphtheria, tetanus and pertussis. In infants the dose of 3 drops of vaccine may be administered directly into the mouth, whilst in children it may be given in a spoonful of syrup or on a sugar lump. It has been shown that breast-fed infants of 3 months of age respond with a satisfactory immunity to OPV and there is no need to delay its administration at this age. The vaccine should also be offered to the parents if they are unimmunised.

6.3.2 Inactivated poliovaccine (IPV) is available for primary immunisation in persons for whom a live vaccine is contra-indicated. Since IPV contains traces of penicillin it should not be given as a substitute to individuals who are sensitive to penicillin. Three doses of 0.5ml should be administered by deep subcutaneous or intramuscular injection with the same time intervals as for OPV.

6.3.3 *Post-primary immunisation*

A reinforcing dose of oral poliomyelitis vaccine (OPV) should be given at school entry or entry to nursery school. For convenience this may be given at the same time as the reinforcing dose of diphtheria and tetanus vaccine.

6.3.4 A further reinforcing dose of OPV or IPV should be given at 15-19 years of age on leaving school or before employment. *It is not necessary to offer further reinforcing doses to adults unless they are likely to be exposed to special risk of contracting the disease.* Those at special risk include:-

a. travellers to areas or countries where poliomyelitis is epidemic or endemic,

b. health care workers in contact with poliomyelitis cases.

6.3.5 Reinforcing doses are necessary every 10 years to maintain protection.

6.3.6 *Primary immunisation of adults*

A basic course of three doses of poliomyelitis vaccine at intervals of 4 weeks is recommended for the primary immunisation of adults who are at special risk of exposure to poliovirus. Unvaccinated parents of children who are to be given OPV should be offered a basic course of vaccine.

6.4 Side-effects and adverse reactions

6.4.1 The results of the Public Health Laboratory Service surveillance scheme, in operation since 1962 in England and Wales, have been reviewed regularly by the Joint Committee on Vaccination and Immunisation. Cases of "vaccine-associated"

poliomyelitis have been reported in recipients of OPV and in contacts of recipients since 1962. From 1962-1977, 72 cases were reported, representing an incidence of approximately one in three million doses administered. The JCVI have concluded that the possibility of a very slight risk of poliomyelitis induced by the oral vaccine cannot be ruled out, but that the likelihood is so small that it is unjustifiable to place any restriction on the programme at present recommended in the United Kingdom.

6.4.2 Severe reactions observed following immunisation with poliomyelitis vaccine should be reported to the Committee on Safety of Medicines using the yellow card system.

6.5 Contra-indications

6.5.1 The general contra-indications to live vaccines apply to oral poliomyelitis vaccine and should be observed. These are:-

a. Vaccination should be postponed if the patient is suffering from a febrile illness.

b. Patients receiving corticosteroid or immuno-suppressive treatment, including general radiation.

c. Patients suffering from malignant conditions such as lymphoma, leukaemia, Hodgkin's disease and other tumours of the reticuloendothelial system and where the normal immunological mechanism may be impaired as for example in hypogammaglobulinaemia.

d. Although adverse effects on the fetus have not been reported, oral polio vaccine should not normally be given to women during the first 4 months of pregnancy unless there are compelling reasons.

6.5.2 If it is necessary to administer more than one live virus vaccine at the same time, they may be given simultaneously at different sites (unless a combined preparation is used). If not given simultaneously, administration of live virus vaccines should be separated by an interval of at least 3 weeks. It is also recommended that a 3 week interval should be allowed between the administration of OPV and the giving of BCG.

6.5.3 Oral poliovaccine should not be given if the recipient is suffering from diarrhoea or other intestinal upset. Both vaccines might contain traces of antibiotics but these do not normally contra-indicate use except in extreme cases of hypersensitivity. OPV contains polymyxin, neomycin, penicillin and streptomycin, whilst IPV contains, penicillin, neomycin and streptomycin.

6.5.4 It is advisable to allow at least three weeks to elapse between undergoing tonsillectomy or oral surgery and the administration of OPV.

6.5.5 OPV is not contra-indicated for breast fed infants; studies have demonstrated that breast feeding does not inhibit the development of antibodies to OPV.

6.6 Management of outbreaks

6.6.1 On the occurrence of a single case of paralytic poliomyelitis, it is recommended that a dose of oral poliomyelitis vaccine should be given to all persons in the neighbourhood of the case (with the exception of people suffering from immunodeficiency) regardless of the previous history of immunisation against poliomyelitis. If it is possible to implicate a vaccine-derived poliovirus as the cause of the case then no vaccination plan needs to be developed, as no outbreaks associated with vaccine virus have been documented to date. If the source of the outbreak is uncertain then it should be assumed to be a "wild" virus, and appropriate control measures instituted.

6.7 Supplies

6.7.1 a. Oral poliomyelitis vaccine (OPV) (Pol/Vac/Oral) contains live attenuated strains of poliomyelitis virus, types I, II and III grown in cultures of monkey kidney cells. It is packaged in dropper tubes of 10 doses. Manufactured by the *Wellcome Foundation Ltd and **Smith, Kline and French Ltd.

b. Inactivated poliovirus (IPV) contains poliovirus types I, II and III grown in monkey kidney cell cultures and inactivated with formalin and supplied in single dose 1ml ampoules. Manufactured by **Smith, Kline and French Limited. Obtained from DHSS, 14 Russell Square, London WC1B 5EP (phone 01-636 6811) or to Welsh Office, Grayfriars Road, Cardiff.

***Wellcome - Tel: Crewe (0270) 583151**
****Smith Kline and French Tel: Welwyn Garden 01-962 5111**

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IMMUNISATION AGAINST INFECTIOUS DISEASE

7. MEASLES

7.1 Introduction

7.1.1 Measles is an acute viral illness transmitted via the respiratory tract. It is characterised by such clinical features as Koplik spots, coryza, conjunctivitis, bronchitis, skin rash and fever. The incubation period is about 10 days, with a further 4 days before the rash appears. It is highly infectious from the beginning of the prodromal period to 4 days after the appearance of the rash. In about 1 in 15 cases complications may occur; these include otitis media, pneumonia, convulsions and encephalitis. The incidence of serious neurological complications varies between different surveys, but is probably in the order of 1 in 5000 cases. It is known that electro-encephalographic changes may occur during apparently unprotected measles as well as in cases with frank encephalitis. Complications are more common and severe in poorly nourished, chronically ill and very young children; this is particularly true in developing countries.

7.1.2 Notification of measles was introduced in England and Wales in 1940, and until the introduction of vaccine in 1968 the average yearly total varied between 160,000 and 800,000 cases, the peaks occurring in two year cycles. By the mid-seventies notifications had fallen to about 50-180,000 cases with a less marked periodicity. Mortality attributable to measles has been declining throughout the century. In 1900 over 12,000 deaths were recorded but this had fallen to around 1000 a year by 1940 and to about 90 by 1968. Since the introduction of vaccination this decline has continued, to an average of 20 deaths a year, the majority in physically disabled children often those with genetic defects.

7.1.3 Since 1968 vaccine acceptance for children in the second year of life has remained at about 50% in England. The fall in measles notifications has been most marked in the 1 - 4 and 5 - 9 year age groups while notifications in older children and adults are so far unaffected.

7.2 Measles vaccine

7.2.1 The vaccine recommended for routine vaccination against measles since 1969 is a freeze-dried preparation containing live attenuated measles virus. (Attenuvax, Mevilin-L and Rimevax).

It should be stored in the dried state at 2-8°C. It is reconstituted immediately before use with the diluent fluid (water) supplied by the manufacturers and 0.5ml is administered by deep subcutaneous or intramuscular injection. Vaccination results in sero-conversion in 95 per cent of recipients. Vaccine induced antibody titres tend to be lower than those following natural infection, but have nevertheless been shown to persist for at least 16 years. The degree to which these levels are reinforced by subsequent exposure to natural measles in the community is not known. The attenuated vaccine virus is not excreted after vaccination and thus there is no risk of infection from vaccine recipients.

7.3 Recommendations

7.3.1 In order to achieve the maximum benefit, measles vaccination should be offered routinely in the second year of life. This will usually be after completion of the primary course of immunisation against diphtheria, tetanus, whooping cough and poliomyelitis. However, if the third injection of the primary course has been delayed measles vaccine can be given before the primary course is completed. Vaccination is recommended for all unprotected children from the second year of life.

7.3.2 Serological studies in children with a history of measles in early life have demonstrated that a diagnosis in children under the age of 24 months was in a large proportion of cases incorrect. It is therefore recommended that a previous history of measles in the first 2 years of life should not be regarded as a contra-indication to measles vaccination.

7.3.3 It is important to recognise that unimmunised children in the following groups are at particular risk from measles infection and therefore vaccination is strongly recommended:-

a. children with chronic conditions affecting physical development (*eg:* cystic fibrosis, congenital heart disease)

b. children from the age of one year upwards in residential care

c. children entering playgroups, nursery school, school or other establishments accepting children for day care

7.3.4 Live measles should not be given routinely to children below the age of 12 months since it may fail to immunise in that age group owing to the presence of maternally transmitted antibodies. However, when a young infant is exposed or is likely to be exposed to natural measles, normal immunoglobulin can be used either to abort or modify the attack but where this is done it is necessary that vaccination be given at 12 to 15 months of age to ensure adequate immunity.

7.3.5 In older children, as antibody develops more rapidly following the administration of measles vaccine than the natural disease, vaccine can be used to protect susceptible contacts. This is particularly useful in home contacts and in susceptible children in schools and hospitals. The vaccine must be administered within three days of exposure, provided that there are no contra-indications to its use.

7.3.6 A single dose of live measles vaccine should be administered in the volume recommended by the manufacturer. Re-vaccination is only necessary when vaccination occurred before 12 months of age. Children with a personal history of convulsions or whose parents or siblings have a history of idiopathic epilepsy, should be given measles vaccine but only with the simultaneous administration of specially diluted human normal immunoglobulin for use with measles vaccine.

7.3.7 The dilute immunoglobulin contains 19 International Units (IUs) measles antibody in 1.8 ml. The recommended dose is 0.4 to 0.8 IU/kg body weight. Hospital pharmacies should hold a small stock of this product otherwise it can be obtained from The Blood Product Laboratory Elstree (Phone 01-953 6191).

7.3.8 Routine primary immunisation of adults is not necessary because they are very likely to have acquired immunity by natural infection.

7.4 Side-effects and adverse reactions

7.4.1 Adverse reactions to measles vaccine are very few when compared with the incidence of complications of natural measles. The vaccine usually produces a subclinical infection in vaccinees. The most common reaction is malaise and fever, with or without rash, occurring 5-10 days after administration of the vaccine. This febrile reaction, when it occurs, seldom lasts more than

24-48 hours and vaccine virus is not transmitted to contacts. Febrile convulsions may occur during such episodes in a very small number of children aged 1-2 years, particularly if there is a simultaneous intercurrent infection. However, the incidence of convulsions is 8 to 10 times less than the incidence occurring as a result of measles infection.

7.4.2 Encephalitis is a rare complication of measles vaccine, and as with convulsions, the incidence is considerably less than occurs with natural infection. Cases of sub-acute sclerosing panencephalitis (SSPE) have been reported in individuals who have no history of measles, and a few of these patients have received live attenuated measles vaccine. However, the risk of developing SSPE following vaccination appears to be about one-tenth of the risk associated with natural infection; *thus measles vaccination significantly reduces the risk of both SSPE and measles encephalitis.*

7.4.3 Allergic reactions to measles vaccine may occur and as a precaution a solution of 1 in 1,000 adrenaline BP should always be readily available.

7.4.4 Initial dose 0.5 ml for adults. For young children the initial dose is:

0.05 ml for infants aged 3 - 5 months
0.075 ml for infants aged 6 - 11 months
0.1 ml for infants aged 1 year

7.4.5 Adrenaline BP should be given by intramuscular injection.

7.4.6 It is very important that any severe reaction following the administration of measles vaccine, whether or not considered to be due to vaccine, should be reported without delay to the Committee on Safety of Medicines using the yellow card system.

7.5 Contra-indications

7.5.1 Vaccination should be postponed in individuals suffering from a febrile illness, particularly respiratory. Measles vaccine is a live virus vaccine and the contra-indications to these vaccines should be observed. Vaccination should be avoided in:-

a. patients receiving corticosteroid or immunosuppressive treatment, including general radiation;

b. patients suffering from malignant conditions such as lymphoma, leukaemia, Hodgkin's disease or other tumours of the reticulo-endothelial system or where the normal immunological mechanism may be impaired as for example in hypogammaglobulinaemia;

c. pregnant women because of the theoretical risk of fetal infection. There is no evidence in practice to substantiate this risk.

7.5.2 If it is necessary to administer more than one live virus vaccine. The vaccines should be given simultaneously at different sites (unless a combined preparation is used), or separated by an interval of at least 3 weeks. It is also recommended that a 3 week interval should be allowed between the administration of live virus vaccines and the giving of BCG.

7.5.3 Measles vaccine should not be given to persons hypersensitive to neomycin or polymyxin. The vaccine contains no penicillin. Allergy to hens' eggs is no longer considered to be a contra-indication to the vaccine except in patients with severe hypersensitivity. Individuals with a history of anaphylactoid reactions to egg ingestion (generalised urticaria, swelling of the mouth and throat, difficulty in breathing, hypotension and shock) should not be given measles vaccine. Persons who have allergies to egg that are not of an anaphylactoid nature and those with allergies to chicken feathers may be vaccinated in the usual manner.

7.5.4 Measles virus inhibits the response to tuberculin, so tuberculin-positive individuals may become tuberculin-negative for up to a month after infection or immunisation with measles virus. Exacerbation of tuberculosis might occur with measles or measles vaccine, and therefore individuals known to have active tuberculosis should be under treatment when vaccinated.

7.6 Management of outbreaks

7.6.1 The spread of measles can be contained by the vaccination within 72 hours of susceptible children who have been in contact with an infected case. If there is doubt about a child's measles immunity, the vaccine should be given, since there are no ill-effects from vaccinating those already sero-positive. Human normal immunoglobulin is available for individuals for whom the live vaccine is contra-indicated. Children under the age of one

year should receive human normal immunoglobulin and those who have immuno-suppressed conditions should receive human normal immunoglobulin with a specific content of measles antibody. Dose : under 1 year 0.25 g : 1-2 years 0.5 g : over 3 years 1.5 g.

7.7 Supplies

7.7.1 Live attenuated measles vaccine (Meas/Vac(Live)) is a freeze-dried preparation of living attenuated virus issued in single-dose vials (0.5 mls) with water diluent. Vaccines of the Schwarz strain are manufactured by Duncan, Flockhart & Co Ltd - Mevlin - (Tel. No. 01-739 3451) and by Smith, Kline and French Ltd - Rimevax (Tel. No. Welwyn Garden 25111). A vaccine of the Moraten strain in manufactured by Merck, Sharp and Dohme Ltd. - Attenuvax (Tel. No. Hoddesdon (0992) 467272). Human normal immunoglobulin with a specific content of measles antibody is available from Regional Transfusion Centres in England and Blood Transfusion Centres in Scotland, and Wales - manufactured by Blood Products Laboratories, Elstree, (Tel. No. 01-953 6191), and the Protein Fractionation Centre, Ellen's Glen Road, Edinburgh, EH17 7QT (Tel. No. 031-664 2317).

7.7.2 Specially diluted human normal immunoglobulin with a specific content of measles antibody is obtainable from The Blood Products Laboratory Elstree (phone 01-953 6191).

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IMMUNISATION AGAINST INFECTIOUS DISEASE

8. TUBERCULOSIS
BCG VACCINATION

8.1 Introduction

8.1.1 Tuberculosis, which is caused by *Mycobacterium tuberculosis* or *Mycobacterium bovis* may affect any part of the body but infection is usually acquired via the respiratory route. The incidence of the disease has declined over the years in England and Wales, and to a lesser extent in Scotland, but this has now levelled out and new cases are still occurring especially in the big conurbations. Particular consideration should be given to immigrants from developing countries who may be at special risk.

8.2 Bacillus-Calmette-Guerin (BCG) Vaccine (Intradermal)

8.2.1 BCG vaccine (intradermal) is supplied as a freeze-dried vaccine with diluent provided in a separate ampoule. It is available free of charge on application to the Supply Division of the appropriate National Health Department. Surveys in British school children have shown that the vaccine is over 70% effective, with protection lasting at least 15 years.

8.3 Vaccination

8.3.1 The dosage of BCG is 0.1 ml of vaccine injected intradermally, for infants the dose should be reduced to 0.05 ml; the injection must be given strictly intradermally and not subcutaneously (see 8.7.3 for details of technique). The use of a separate needle and syringe for each patient is recommended to avoid the possible risk of transmission of hepatitis. The site of inoculation is usually in the area over the insertion of the left deltoid muscle. The tip of the shoulder should be avoided. In girls, for cosmetic reasons, the upper and lateral surface of the thigh may be preferred. Apart from new-born children, any person who is being considered for BCG vaccination should first have a test for hypersensitivity to tuberculo-protein.

8.4 Recommendations

8.4.1 It is recommended that the following groups should be vaccinated if found to be negative for tuberculo-protein hypersensitivity:-

a. Contacts of cases known to be suffering from active respiratory tuberculosis; the children of immigrants in whose communities there is a high incidence of tuberculosis may for this purpose be regarded as contacts. New-born infant contacts need not be tested for sensitivity but should be vaccinated without delay.

b. Health Service Staff; this category should include not only medical students, hospital medical staff, nurses, but anybody who comes into contact with patients, including physiotherapists and radiographers, technical staff in pathology departments and any others considered to be at special risk because of the likelihood of contact with infective patients or their sputum. It is particularly important to test staff working in maternity and paediatric departments.

c. School children between their 10th and 14th birthdays.

d. Students (including those in teacher training college)

8.4.2 *NB.* After inoculation with present BCG vaccine there is a high conversion rate and only staff who have a high risk of contact with tuberculous patients and tuberculous pathological material need further observation. Staff in this high risk group should have the site of vaccination inspected six weeks after inoculation to confirm that a satisfactory reaction has occurred. Only those who show no evidence of a satisfactory reaction require a post BCG tuberculin test. Those who are tuberculin negative should be re-vaccinated and if there is still no evidence of a satisfactory reaction or conversion to a positive tuberculin test they should be employed elsewhere in the Health Service where they are unlikely to be exposed to tuberculosis. They must not handle tuberculous material until found to be either tuberculin positive or have demonstrated a satisfactory reaction to vaccination. The normal time to carry out a post vaccination test is 6 - 12 weeks after vaccination.

8.5 **Testing for Hypersensitivity to Tuberculo-Protein** (Tuberculin Testing)

8.5.1 **Hypersensitivity testing techniques**

Except in the case of new-born children, this testing is always undertaken when BCG vaccination is being considered in order

that an assessment may be obtained of the individual's sensitivity to tuberculo-protein. To ensure uniformity of results it is desirable to use the official supply of a purified protein derivative (PPD) which is available, free of charge, on application to the appropriate Health Department. All PPD tuberculin should be stored at 2^{o} - 8^{o}C and protected from light. Once an ampoule has been opened any contents should be used within one hour and in any case should not be kept longer than one morning or afternoon session.

8.5.2 **The Intradermal Test** (Mantoux Test)

In carrying out the test an area of skin, usually over the upper third of the flexor surface of the forearm, is cleaned with spirit and 0.1 ml of tuberculin PPD, BP 1 in 1000, is injected intradermally so that a wheal is produced of about 7 mm in diameter. The result should be read after 72 hours but usually a valid reading can be obtained up to 96 hours. A positive result consists of an induration of not less than 6 mm in diameter.

8.5.3 The PPD preparation supplied for the Mantoux test is a 1 : 1000 dilution of Tuberculin PPD solution and it contains 10 Tuberculin Units (TU) in a dose of 0.1 ml. The dilution is supplied in 1.0 ml volumes in ampoules, the contents of an ampoule being sufficient for about 8 tests. The preparation should not be used after its expiry date. If Tuberculin is required for tests in patients in whom tuberculosis is suspected the commercially available 1 in 10,000 dilution containing 1 TU in 0.1 ml should be used.

8.5.4 **The Multiple Puncture Test** (Heaf Test)

a. The results of the Heaf multiple-puncture test are expressed as Grades 1-4 (see below). Various estimates have been made of the correlation between Mantoux test results and these grades. As an approximation, a positive reaction to 10 TU and a Heaf test response intermediate between Grade 2 and Grade 3 can be taken as equivalent. For this test the Heaf Multiple Puncture Apparatus is used. A puncture of 2 mm depth is recommended for all ages over two years; under that age a puncture of 1 mm is sufficient.

b. PPD for this test is supplied in 1 ml ampoules in packs of five each containing 1 ml of solution at a strength of 2.0 mg Tuberculin PPD per ml. One ampoule

of this material should suffice for between 50 and 100 tests. The PPD should not be used beyond the expiry date.

c. This Tuberculin PPD of special strength (for Heaf testing) is applied to a clean dry area of the forearm with a sterile glass rod, platinum loop or needle attached to a syringe which should not be allowed to come into contact with the skin. The PPD is smoothed over by the end plate of the apparatus, which is then pressed firmly at right angles to the skin surface over the area and the needles released. Excess PPD is then removed.

d. Results may be read any time from 3 to 10 days after puncture. A positive result should be recorded only when there is a palpable induration around at least four puncture points. Grades are defined as follows in the Heaf test:-

Grade 1	at least 4 small indurated papules
Grade 2	an indurated ring formed by confluent papules
Grade 3	a solid induration 5 to 10 mm wide
Grade 4	induration over 10 mm wide

e. It is now generally accepted that Grade 1 reactions in individuals who have not previously received BCG vaccination are not usually related to infection with *M. tuberculosis* and they may therefore be offered the vaccination.

f. Disinfection of the multiple puncture apparatus is most conveniently done by wetting the end plate and the needles by dipping them into methylated spirit, held in a suitable container. The spirit which adheres to the apparatus is then ignited. Both the end plate and the needles must be flamed. This is accomplished by holding the apparatus at an angle between horizontal and vertical with the end plate being directed upwards while flaming. Care must be taken not to allow the needles to become too hot while excess spirit burns off.

8.5.5 Nurses or health visitors, specially trained in the techniques involved and working under the supervision of an experienced doctor, may be employed to perform the sensitivity tests and to read and record the results.

8.6 Positive Reactors

8.6.1 Those with strongly positive reactions to a test for hypersensitivity to tuberculo-protein should be referred for further investigation and supervision. A strongly positive reaction may be defined as 15 mm or more induration after a Mantoux test of 10 TU, or a Grade 3 or 4 reaction to the Heaf test.

8.7 Side effects and adverse reactions to BCG Vaccine

8.7.1 Normally a local reaction develops at the site of the vaccination in from two to six weeks. It begins as a small papule which slowly increases in size for two to three weeks; occasionally a shallow ulcer up to 10 mm in diameter may develop. If this discharges; a temporary dry dressing may be used until a scab forms but it is essential that air should not be excluded. The lesion slowly subsides after about two months, and eventually heals leaving only a small scar. An impermeable dressing should only be applied for a very short period for example to permit swimming, as it can delay healing and result in a large scar.

8.7.2 *Faulty injection technique is the most frequent cause of severe injection site reactions* (large ulcers and abscesses).

8.7.3 In order to ensure that these are reduced to a minimum, it is necessary for vaccinators to be familiar with interpreting the results of tuberculin tests and also to be skilled in the technique of intradermal injection. When giving an intradermal injection the operator should stretch the skin between thumb and forefinger of one hand and with the other slowly insert the needle, with the bevel upwards, for about 2 mm into the superficial layers of the dermis almost parallel with the surface. The needle should be short, with a short bevel which can usually be seen faintly through the epidermis during insertion. A raised, blanched, bleb showing the tips of the hair follicles is a sign that the injection has been made correctly and its diameter gives a useful indication of the amount which has been injected. A bleb of 7 mm diameter is approximately equivalent to 0.1 ml.

8.7.4 Considerable resistance is felt from a correctly given intradermal injection; if this is not felt and it is suspected that the needle is too deep, it should be removed and reinserted before more vaccine is given. The use of jet injectors is not recommended.

8.7.5 Complications following BCG vaccination apart from these injection site reactions, are rare and mostly consist of adenitis with or without suppuration and discharge. A minor degree of adenitis may occur in the weeks following vaccination and should not be regarded as a complication. Very rarely a lupoid type of local lesion has been reported. A very few cases characterised by widespread dissemination of the injected organisms have been reported. Anaphylactic reactions can occur.

8.7.6 It is important that all complications should be noted and a full record kept. Serious or unusual complications including abscess and keloid scarring should be reported to the Committee on Safety of Medicines using the yellow card system. Every effort should be made to recover the causative organism from any lesion constituting a serious complication and have it identified. Any complications following vaccination should be referred to a chest physician.

8.8 Contra-indications and precautions

8.8.1 BCG vaccine should not be given to:-

a. Patients receiving corticosteroid or immunosuppressive treatment, including general radiation, those suffering from malignant conditions such as lymphoma, leukaemia, Hodgkin's disease or other tumours of the reticulo-endothelial system or those in whom the normal immunological mechanism may be impaired eg, as in hypogammaglobulinaemia.

b. In pregnancy, particularly the early stages because of possible harm to the fetus. However, where there is a significant risk of infection the importance of vaccination may outweigh the possible risk to the fetus.

c. Persons with positive sensitivity tests to tuberculo-protein. (Those with Heaf Grade 1 reactions, unless previously vaccinated, may be regarded as tuberculin negative and, in the absence of contra-indications, offered vaccination.)

d. Persons with pyrexia.

e. Persons suffering from septic skin conditions or eczema at the proposed vaccination site.

8.8.2 An interval of at least three weeks should normally be allowed to elapse between the administration of BCG vaccine and any other live vaccine, whichever is given first. No further immunisation should be given for at least three months in the arm used for BCG vaccination because of the risk of regional lymphadenitis.

8.8.3 Even if performed in the few weeks after exposure to infection before tuberculin sensitivity has developed, vaccination will do no harm. An awkward clinical problem can arise if when vaccinating a contact, symptoms develop shortly afterwards, because of the difficulty in interpreting a positive tuberculin test. There is therefore some advantage in delaying BCG vaccination of a contact, having segregated the individual from the source of infection until about six weeks after the last known contact, repeating the skin test then and vaccinating only if this is still negative. However, it is better to vaccinate without segregation than not to vaccinate at all. If in such circumstances isoniazid is to be administered prophylactically, the use of isoniazid-resistant BCG vaccine, which is available, should be considered.

8.9 Record keeping and surveillance

8.9.1 It is important that individual records should be available to show the BCG vaccination state of an individual and whether he was tuberculin positive when last tested. It is desirable that records of vaccination with BCG and of sensitivity testing should be completed for every person vaccinated under the Health Authority's arrangements and the records should be kept for at least 10 years.

8.9.2 BCG vaccination of hospital staff and medical and dental students should be recorded on the appropriate form. If a member of the staff or a student moves to another hospital or to another medical or dental school, the record card should be sent there.

8.10 Supply

8.10.1 Supplies of BCG vaccine (intradermal) are distributed to users once a month. The vaccine is normally issued in ampoules of 10 doses and the titre is 8-26 x 10^6 viable units per ml. *Dried BCG vaccine shoud be stored at 2° - 8°C and protected from light. It should not be used after the expiry date stated on the label. The ampoule should be opened using suitable aseptic precautions and the contents should be used within one hour of reconstitution and in any case should not be kept longer than one morning or afternoon session.* Orders covering at least one month's requirement should be submitted on the user's own order form to reach the appropriate supply department not later than the first day of the month preceding the month in which the supply is to be used; for example, orders for supply for use in August should reach the appropriate supply department not later than 1 July. Orders should be sent as follows:-

Users in England (Tuberculin PPD and Dried BCG vaccine) (intradermal)	Department of Health & Social Security (DSB2) 14 Russell Square London WC1B 5EP (Tel. 01-636 6811)
Users in Scotland (Tuberculin PPD)	The Central Infusion Fluids Laboratory Knightswood Hospital Glasgow W3 (Tel. 041-954 9641)
Users in Scotland (Dried BCG vaccine) (intradermal)	The Scottish Health Service Common Services Agency Supplies Division Trinity Park House South Trinity Road Edinburgh EH5 3SH (Tel. 031-552 6255)
Users in Wales (Tuberculin PPD and Dried BCG vaccine) (intradermal)	The Welsh Office Health & Social Work Department Pearl Assurance House Grayfriars Road Cardiff CF1 3RT (Tel. 0222 44151)

9. RUBELLA

9.1 Introduction

9.1.1 Rubella is generally a mild childhood infectious disease, causing a transient erythematous rash, lymphadenopathy involving post auricular and sub-occipital glands and occasional joint involvement including arthritis and arthralgia. Symptoms are often so fleeting as not to be recognised clinically. More serious complications such as neurological disorders and thrombocytopenia may occur but are rare. These same symptoms can also be caused by viruses other than rubella virus and clinical diagnosis is therefore quite unreliable. The incubation period is from 14-21 days and the period of communicability is from 1 week before until at least 4 days after the onset of the rash.

9.1.2 A relationship between maternal rubella and congenital defects was first recognised in the 1940s and showed that there was a need to prevent pregnant women from contracting the disease, particularly early in pregnancy. Maternal rubella infection during the first trimester is the period of greatest risk for the fetus but there is also a small risk particularly as regards hearing defects and delayed development following maternal infection up to the 20th week. Some observers have reported defects between the 20th and 24th week of pregnancy.

9.1.3 Congenital rubella presents a wide spectrum of defects. Not only may the heart, eyes and ears be affected but frequently there is intra-uterine growth retardation with involvement of CNS, haemopoetic system (causing thrombocytopenia and purpura), liver, lungs, bones and the myocardium. Multiple defects are extremely common. The only defects that are commonly encountered alone are perceptive deafness and pigmentary retinopathy. The mode of presentation may be extremely variable depending on the age at which intra-uterine infection occurs and the extent of the fetal damage. Hearing and developmental defects may not be detected for some months or years.

9.1.4 The rubella virus was isolated in cell cultures in 1962 and effective vaccines have been prepared from strains of attenuated virus in either rabbit kidney or human diploid cells. These have been licensed in the United Kingdom since 1970.

9.2 Rubella vaccine

9.2.1 Live attenuated rubella virus vaccine is available as a freeze dried preparation; diluent is provided in a separate ampoule. Single-dose or multi-dose containers are available and should be stored at domestic refrigeration temperatures (2° - 8°C). The freeze dried pellet is reconstituted with the diluent provided using a sterile dry syringe and injected as soon as possible after reconstitution but in any event not after more than 1 hour at room temperature in order to ensure that potency is maintained.

9.2.2 The dosage is 0.5 ml administered by deep subcutaneous or intramuscular injection for both children and adults. A single dose induces antibodies in approximately 95 per cent of susceptible persons. Vaccine induced antibody has shown little decline in the 16 years follow-up of girls who were among the first to receive the vaccine. It is expected that protection against clinical rubella will be long term.

9.2.3 Re-infection with rubella virus may occur in those persons with low antibody titres following vaccination or primary infection with wild virus. However, a re-infection in an immune subject does not appear to be a hazard to the fetus.

9.2.4 Vaccine virus has been shown to be excreted in the nasopharynx of vaccinated persons in small amounts, usually during the second or third week after vaccination, but numerous studies in closed communities have failed to provide conclusive evidence that infection is transmitted from vaccinated persons to susceptible contacts. It is considered that there is no risk of pregnant women contracting rubella from recently vaccinated individuals.

9.3 Recommendations

9.3.1 i. All girls between their 10th and 14th birthdays (that is aged 10, 11, 12 and 13 years) should be routinely offered rubella vaccine. *A history of a previous attack of rubella should be disregarded in view of the difficulty of being certain of the diagnosis.*

ii. All seronegative women of child-bearing age, provided they are not pregnant, should be offered rubella vaccine. As rubella vaccine virus can cause fetal infection,

it is essential that the vaccine should NOT be administered to any woman who may be pregnant. *Those administering the vaccine should be careful to instruct women to whom it is given that they should not become pregnant within 3 months of vaccination.*

9.3.2 In view of the potential risk to the fetus from vaccination, it is desirable to carry out blood tests on women to determine their rubella immune status. The reason for doing this is as follows: approximately 80 per cent of women of child-bearing age are already immune to rubella as a result of natural infection and thus do not require to be vaccinated as natural immunity is so effective. Unless the immune status of a woman who has been vaccinated and who is subsequently found to be pregnant is known prior to vaccination, then it must be assumed that she was non-immune and that the fetus is at risk. Screening will reveal those who are already immune, thus reducing the total number of women who are vaccinated by approximately 80 per cent and therefore the number of pregnancies in which terminations may have to be considered.

9.3.3 *Women found to be seronegative as a result of the blood test should be vaccinated taking all contra-indications (paragraphs 9.5.1/2) into account. All women should be informed of their immune status.*

9.3.4 Certain groups of women such as school teachers, nursery and play group staff, community health staff, all nurses and doctors who work in children's hospitals and in obstetrics and gynaecological units may be at special risk of contracting rubella from children or from infected fetal material. Staff and students, both male and female, working in antenatal clinics may, if they become naturally infected, transmit rubella to patients in the early stage of pregnancy. Individuals in all these groups should have their antibody status determined and, if found to be seronegative, should be offered vaccination both for their own protection and for the protection of seronegative pregnant patients.

9.4 Side effects and adverse reactions

9.4.1 Mild reactions, which include fever, sore throat, lymphadenopathy, rashes and arthralgia or arthritis, may occur following vaccination. Symptoms, when they do occur, usually begin 1-3 weeks after vaccination and are normally transient;

joint symptoms are more common in women than in young girls. Neurological symptoms such as peripheral neuropathy have been reported following rubella vaccination but a casual relationship has not been established. *Serious reactions observed following rubella vaccination should be reported on yellow cards to the Committee on Safety of Medicines.*

9.5 Contra-indications

9.5.1 Rubella vaccine is a live virus vaccine and the contra-indications to these vaccines should be observed, namely:

a. Vaccination should be postponed if the patient is suffering from a febrile illness until recovery is complete.

b. Pregnancy is an absolute contra-indication to rubella vaccination and should be avoided for 3 months following vaccination.

c. The vaccine should not be administered to patients receiving cortico-steroid or immunosuppresive treatment, including general radiation, or to those suffering from malignant conditions such as lymphoma, leukaemia, Hodgkin's disease or other tumours of the reticulo-endothelial system, or where the normal immunological mechanism may be impaired as, for example, in hypogammaglobulinaemia.

d. If it is necessary to administer more than one live virus vaccine at the same time, they may be given simultaneously at different sites (unless a combined preparation is used). If not given simultaneously they should be separated by an interval of at least 3 weeks. It is also recommended that a 3-week interval should be allowed between the administration of a live virus vaccine such as rubella vaccine and BCG.

9.5.2 Rubella vaccines currently in use are produced either in human diploid cell cultures (Almevax and Meruvax), or in rabbit kidney cell cultures (Cendevax). Rubella vaccines may also contain traces of antibiotics (neomycin and/or polymyxin). Account should therefore be taken of possible hypersensitivity to rabbit protein or fur in the case of Cendevax and also to these antibiotics. The manufacturer's leaflet gives information on the specific contra-indications for each vaccine and it is important that these are studied.

9.6 Management and surveillance

9.6.1 It is part of the vaccination policy that all women attending for antenatal advice should be tested for immunity to rubella and every effort made to ensure that the vaccine is administered post partum to those found to be seronegative. Wherever possible the vaccine should be given before the woman is discharged from the maternity unit. In the rare cases when a woman requires simultaneous administration of rubella vaccine and anti-D immunoglobulin, the two products can be administered at the same time provided separate syringes are used, and the products are administered into contra-lateral limbs, but a blood test should be performed not earlier than 8 weeks later to see that rubella antibodies have been produced. If it has been necessary to give a blood transfusion, vaccination should be delayed for 3 months to allow time for the elimination of rubella antibody possibly present in the donated blood. *If possible all women who have been sero-tested should be informed in writing about their immune status and given a record card with details of any vaccination.*

9.6.2 Whilst the policy of vaccinating schoolgirls should eventually protect most women from contracting rubella during pregnancy, it is important in the meantime to vaccinate women of child-bearing age who are susceptible. Every opportunity for offering vaccine to these women should be taken when they attend their family doctor or clinics for advice on family planning. It may also be possible to arrange for screening when medical examinations are carried out for employment purposes or at further education training establishments. Girls who leave school without having been vaccinated should, where possible, be sero-tested and vaccinated where necessary, by arrangement with their general practitioner.

9.6.3 In order to monitor the success of the rubella vaccination policy, any child with congenital rubella defects or with symptoms suggestive of having been caused by rubella should be notified to the National Congenital Rubella Surveillance Scheme. There are two Central Registries to record cases or suspected cases of congenital rubella, these are:

a. For the following Regions: Thames, Wessex, South Western, Oxford, East Angiia and Scotland.

Dr Helen Holzel
Department of Microbiology
Hospital for Sick Children
Great Ormond Street
LONDON
WC1N 3JH
(Telephone 01-405 9200, Ext 305)

b. For the following Regions: West Midlands, Trent, Mersey, North Western, Northern, Yorkshire and Wales.

Professor R. W. Smithells
Department of Paediatrics and Child Health
D Floor
The Clarendon Wing
Leeds General Infirmary
Belmont Grove
LEEDS LS2 9NS
(Telephone 0532 432799 ext 3909 or 3900)

9.6.4 These two Central Registries are also conducting surveillance of the effects of rubella immunisation and pregnancy. If any woman is inadvertantly given rubella vaccine in pregnancy, or becomes pregnant within 3 months of immunisation, and the decision is made to continue the pregnancy to term, the outcome of that pregnancy should be recorded. The relevant Central Registry should be notified as early as possible in the pregnancy so that arrangements for the appropriate clinical and virological examination of the new-born infant, and for subsequent follow-up can be made.

9.7 Immunoglobulin

9.7.1 Human immunoglobulin is available for women during the first months of pregnancy who are not known to be immune to rubella and have been in definite close contact with infection. It must be stressed, however, that the use of immunoglobulin cannot be relied upon to protect the mother although it may have a marginal effect on the incidence of abnormalities in the baby. A sample of blood should be taken before administration of the immunoglobulin and a further sample not less than 21 days later so that the rubella antibody status of the mother can be determined. This will provide useful information on which further guidance may be based.

9.7.2 When the use of immunoglobulin in the management of pregnant patients is considered, it is advisable to seek full consultation on the usage and dosage from the Public Health Laboratory Service, from the Community Medicine Specialist (Communicable Diseases) in Scotland, and from the Public Health Laboratory, Belfast City Hospital, in Northern Ireland.

9.8 Supplies

9.8.1 a. A live attenuated RA27/3 rubella virus strain propagated in WI-38 human diploid cells, freeze dried issued with the appropriate diluent manufactured by the Wellcome Foundation Limited. (Almevax).

b. A live attenuated "Cendehill" rubella virus strain propagated in rabbit kidney cells freeze dried issued with the appropriate diluent manufactured by Smith, Kline and French Laboratories Ltd. (Cendevax).

c. A live attenuated RA27/3 rubella virus strain propagated in WI-38 human diploid cells, lyophilised issued with the appropriate diluent manufactured by Thomas Morson Pharmaceuticals (Meruvax).

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IMMUNISATION AGAINST INFECTIOUS DISEASE

12. IMMUNISATION SCHEDULE – NOTES

12.1 Basic course

12.1.1 The basic course of immunisation against diphtheria, pertussis, tetanus and poliomyelitis should begin at 3 months of age and be completed as early as possible because of the need to protect the young infant against pertussis. The maximum response to all three components of triple (DTPer/Vac/Ads) vaccine will be secured if there is an interval of 6-8 weeks between the first and second dose and 4-6 months between the second and third dose.

12.1.2 The recommended schedule is:

1st dose	2nd dose	3rd dose
3 months	4½-5 months	8½-11 months

If whooping cough is prevalent an alternative course of triple vaccine with 1 month's interval between the first and second and second and third doses should be considered. However, such a course be followed at 12-18 months of age by a dose of DT/Vac/Ads vaccine since the intervals of 1 month are considered not to give adequate basic immunity against diphtheria and tetanus.

If the basic course of vaccination is interrupted the course should be resumed with the appropriate subsequent intervals without repetition of earlier doses. If the basic immunisation is commenced after the 6th birthday, pertussis vaccine should be omitted and diphtheria/ tetanus toxoid and oral poliovaccine given.

12.2 Reinforcing doses

12.2.1 Reinforcing doses of diphtheria/tetanus vaccine (DT/Vac/Ads) after the basic course.

12.2.2 There should preferably be an interval of at least 3 years between the last dose of the basic course and the boosting dose of diphtheria/tetanus vaccine which is usually given at school

entrance or at entry to nursery school. A booster dose of tetanus vaccine (Tet/ Vac/Ads) is recommended on leaving school, entering higher education or on commencing employment unless this has been administered within the past 5 years following injury. Reinforcing doses of polio vaccine are advised on school entry, on leaving school, entering higher education or going to work, and for travel abroad to countries where poliomyelitis is endemic.

12.3 Measles vaccine

12.3.1 Measles vaccine should be offered to all susceptible children from the second year of life to puberty. It is important to recognise that the following groups are at special risk:

i. children from the age of 1 year upwards in residential care;

ii. children entering nursery school or other establishment accepting children for day care;

iii. children with serious physical incapacity who are likely to develop severe illness as the result of natural measles infection. Ideally children should be vaccinated against measles during the second year of life. It is strongly recommended that unvaccinated children be vaccinated on entry to a playgroup, nursery school or school.

12.4 BCG vaccine

12.4.1 BCG vaccine is given as a routine to children between their 10th and 14th birthdays who are tuberculin negative irrespective of whether there is a history of BCG vaccination at an earlier age. BCG vaccine should be given at birth to children who come from environments where there is a high risk of contracting tuberculosis, eg. certain immigrant families. Tuberculin negative contacts of known cases of tuberculosis should be given BCG vaccine. Certain virus infections, such as measles, rubella and chickenpox, can suppress the tuberculin test for about 4-6 weeks. For this reason the tuberculin test should not be carried out in the 6 weeks after rubella or measles vaccinations, nor should BCG vaccine be given within 3 weeks after these vaccinations (see note below). Girls are normally offered rubella vaccine at about the same time as BCG. One suggested schedule is to carry out rubella vaccination first and 6 weeks later the tuberculin testing and

BCG programme is carried out. Alternatively, carry out tuberculin testing, read the test and give BCG to the negative responders then wait 3 weeks for rubella vaccination.

12.5 Rubella vaccine

12.5.1 Rubella vaccine may be given to all girls between their 10th and 14th birthdays irrespective of a history of rubella, which cannot be relied upon as evidence of actual immunity. Vaccination is also strongly recommended for adult women of child-bearing age who are seronegative and therefore susceptible. A warning must be given to avoid pregnancy for 3 months after inoculation of rubella vaccine in order to avoid the possible risk of harm to the fetus.

12.6 Oral poliomyelitis vaccine

12.6.1 Unvaccinated parents should be offered oral polio vaccine at the same time as the first dose of oral polio vaccine is given to their baby and arrangements should be made for the parents to complete their basic course of immunisation. If the baby's mother who has not herself received polio vaccine is within the first 4 months of pregnancy, immunisation of the baby should be delayed until the fourth month of pregnancy has passed. If the circumstances are such that immunisation of the baby should not be delayed, ie a risk exists of natural infection from an outbreak, both mother and baby should be given oral polio vaccine.

12.7.1 An interval of not less than 3 weeks should normally be allowed to lapse between the administration of any two live vaccines, unless they are given simultaneously.

SCHEDULE OF VACCINATION AND IMMUNISATION PROCEDURES

This must be read in conjunction with the immunisation schedule notes

Age	Vaccine	Interval	Notes
During the first year of life	DTPer/Vac/Ads and oral polio vaccine (1st dose) DTPer/Vac/Ads and oral polio vaccine (2nd dose) DTPer/Vac/Ads and oral polio vaccine (3rd dose)	*Recommended Schedule* Preferably after an interval of 6-8 weeks Preferably after an interval of 4-6 months *Alternative Schedule* DT/Per/Vac/Ads and oral poliovaccine (1st dose) at 3 months (2nd dose) at 4 months (3rd dose) at 5 months	The first dose of triple vaccine (DTPer/Vac/Ads) together with oral poliomyelitis vaccine (Pol/Vac/(Oral)) should be given at 3 months of age. If pertussis vaccine is contra-indicated or declined by the parent diphtheria tetanus vaccine (DT/Vac/Ads) should be given
During the second year of life	Measles vaccine DT/Vac/Ads at 12-18 months (if alternative schedule is used) (See note 3)	After an interval of not less than 3 weeks following another live vaccine	
At school entry or entry to nursery school	DT/Vac/Ads and oral polio vaccine	It is preferable to allow an interval of at least 3 years after completing the basic course (see note 2)	

Age	Vaccine	Interval	Notes
Between the 10th and 14th birthdays	BCG vaccine	There should be an interval of not less than 3 weeks between BCG and rubella vaccination (see note 4)	For tuberculin negative children. For tuberculin-negative contacts at any age (see note 4)
Between the 10th and 14th birthdays	Rubella vaccine, girls only		All girls of this age should be offered rubella vaccine whether or not there is a past history of an attack of rubella (see note 5)
On leaving school or before employment or entering further education	Polio vaccine (oral or inactivated) and tetanus vaccine (Tet/Vac/Ads)	(See note 2)	
Adult life	Polio vaccine (oral or inactivated) for previously unvaccinated adults	A course for previously unvaccinated adults consists of: Oral polio vaccine: 3 doses with an interval of 6-8 weeks between the first and second doses and of 4-6 months between the second and third; or: Inactivated vaccine: 2 doses at intervals of 6-8 weeks followed by a third dose 4-6 months later (see note 5)	For travellers to countries where poliomyelitis is endemic. Unvaccinated parents of a child being given oral polio vaccine should also be offered a course of oral polio vaccine

Age	Vaccine	Interval	Notes
	Rubella vaccine for susceptible women of child-bearing age		Adult females of child-bearing age should be tested for rubella antibodies, Sero-negative women should be offered rubella vaccination. Pregnancy must be excluded before vaccination and the patient must be warned not to become pregnant for 3 months after immunisation.
	Active immunisation against tetanus (Tet/Vac/Ads) for previously unvaccinated adults	A course for previously unvaccinated adults consists of 3 doses with an interval of 6-8 weeks between the first and second dose followed by a third dose 6 months later.	

IMMUNISATION AGAINST INFECTIOUS DISEASE

13. ANTHRAX

13.1 Introduction

13.1.1 Anthrax is an acute bacterial disease usually affecting the skin, but may rarely involve the lungs or gastrointestinal tract. It is caused by a spore-bearing aerobic bacillus, *Bacillus anthracis,* and is primarily a disease of herbivorous animals. It is infrequent and sporadic in the United Kingdom, affecting workers exposed to infected animal products, including hides, wool and hair, bristle, bone and bonemeal, feeding stuffs and infected livestock and carcasses. Spores may remain alive for many years, and new areas of infection of livestock may develop through introduction of contaminated animal feed. Prevention depends on controlling anthrax in livestock by good industrial practice and by disinfecting imported animal products. Processing of hides, wool and bone by tanning, dyeing, carbonising or acid treatment incidentally ensures that the final product carries no risk of infection but bonemeal used as horticultural fertiliser may contain anthrax spores and those handling it should be advised to wear gloves made of impervious material which should be sterilised or destroyed after use. During the 1970's about 4 cases of human anthrax were reported annually. Deaths from cutaneous anthrax are rare.

13.2 Vaccine

13.2.1 Human anthrax vaccine is the alum precipitate of the antigen found in the sterile filtrate of suitable cultures of the Sterne strain of *Bacillus anthracis* and contains thiomersal as a preservative. It should be kept at 2-8°C and be well-shaken before administration by intramuscular injection.

13.3 Recommendations

13.3.1 Vaccination against anthrax is desirable for workers exposed to special risks of contracting the disease (see Introduction). The recommended dosage of anthrax vaccine is 0.5 ml given intramuscularly on four separate occasions, with intervals of three weeks between the first three doses and an interval of six months between the third and fourth doses. Reinforcing doses of 0.5 ml are advised at yearly intervals.

13.3.2 Other preventive measures should be stressed to workers at special risk. These include the provision of protective clothing and adequate washing facilities, scrupulous medical care of skin abrasions, adequate ventilation and dust control in hazardous industries and the education of workers to ensure prompt medical care of any suspicious skin lesions.

13.4 Side-effects and adverse reactions

13.4.1 Reactions to anthrax vaccine are extremely rare. Mild erythema and swelling lasting up to 2 days may occur at the site of injection. Less frequently regional lymphadenopathy, mild fever, urticaria and other allergic manifestations may occur.

13.4.2 Severe reactions observed following immunisation with anthrax vaccine should be reported to the Committee on Safety of Medicines using the yellow card system.

13.5 Contra-indications

13.5.1 There are no specific contra-indications. The occurrence of a local or general adverse reaction after a first injection of the vaccine does not necessarily indicate a predisposition to subsequent reactions on further injections.

13.6 Management of outbreaks

13.6.1 All cases of anthrax should be notified and an attempt made to confirm the diagnosis bacteriologically. Penicillin is the treatment of choice. Skin lesions should be covered and any discharge or soiled articles require disinfection. Anthrax vaccine has no role in the management of a case or outbreak. An investigation into the source of infection should be carried out.

13.7 Supplies

13.7.1 Anthrax vaccine (Alum precipitated anthrax antigen) contains inactivated Sterne strain anthrax bacilli with thomersal as preservative. Manufactured by *PHLS/CAMR for DHSS. In Scotland supplies are held at the following hospital pharmacies: Bridge of Earn, Law and Peel.

***PHLS - Tel: 01-200 1295**
Centre for Applied Microbiological Research (CAMR) - Tel: 0980-610 391
Bridge of Earn - Tel: 073-881 2331
Law - Tel: 069-83 72621
Peel - Tel: 0896 2295

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14. CHOLERA

14.1 Introduction

14.1.1 Cholera is an acute intestinal disease caused by an enterotoxin produced by *Vibrio cholerae,* Serovar O1 of the classical and El Tor biotypes. Cholera is characterised by sudden onset, profuse watery stools, vomiting, rapid dehydration acidosis and circulatory collapse. Death may occur within a few hours of onset. Mortality ranges from over 50% without treatment to less than 1% with therapy. Inapparent and wholly asymptomatic infections are many times more frequent than clinically recognised cases, especially with El Tor cholera which appears to survive in the environment more readily than the classical type. The incubation period is between 2 and 5 days.

14.1.2 Cholera disappeared from the United Kingdom at the turn of the century, with the last indigenous case having been reported in 1893. The seventh pandemic started in Indonesia in 1961, spread through SE Asia to the Indian sub-continent and the Middle East, reaching Africa, Eastern and Southern Europe by 1971. Between 1970 and 1978, twenty imported cases were reported in England and Wales, but there has been no evidence of spread of infection and no deaths attributed to cholera. Further importation is likely to occur from time to time, but the risk of an outbreak is very small in a country with modern sanitation and water supplies.

14.1.3 Infection is acquired primarily from contaminated water or food. The risk of cholera for travellers who use the usual tourist accommodation is very small.

14.1.4 The currently available cholera vaccine is of limited usefulness. In field trials in endemic areas, the vaccine has been shown to reduce the incidence of overt disease by only about 50% and in addition it fails to prevent people from becoming asymptomatic carriers. Whilst the World Health Organisation (WHO) no longer recommends cholera vaccination for travel to or from cholera infected areas, some countries still require evidence of vaccination having been performed 6 days to 6 months before entry. It is for this reason, and the fact that vaccination may confer some personal protection, that cholera vaccine is available for use by travellers.

CHOLERA

14.2 Vaccine

14.2.1 Cholera vaccine consists of a heat-killed, phenol-preserved mixed suspension of the Inaba and Ogawa sub-types of *Vibrio cholerae,* Serovar O1. Both serotypes are included because they lack full cross-protection. On the basis of field trials in endemic areas, the vaccine is equally effective against both the classical and the El Tor biotypes. The protection conferred persists for 3 to 6 months, but is minimal or non-existent a year after the last dose.

14.2.2 The vaccine should be stored at 2 - 8°C. The currently available vaccine has a tendency, on standing, to settle out in a gelatinous form. Vigorous shaking will yield a homogeneous suspension suitable for injection. Any partly used multi-dose containers should be discarded at the end of the vaccination session.

14.3 Recommendations

14.3.1 Cholera vaccine is indicated for the following:

a. People travelling to countries which require evidence of cholera vaccination. It is recommended that persons travelling abroad should consult with the Embassy or High Commissioner's office for the country in question for current requirements. An International Certificate of Vaccination must be validated for it to be acceptable to quarantine authorities. It is valid for 6 months beginning 6 days after vaccination or beginning on the date of revaccination.

b. People travelling to countries or areas where cholera is endemic or epidemic.

14.3.2 Cholera vaccine is not indicated in the control of the spread of infection or in the management of contacts of imported cases. At the time of vaccination, it should be explained that the best protection against cholera, as well as against many other enteric diseases, is to avoid consuming food and water that might be contaminated. Primary immunisation consists of two doses of vaccine given deep subcutaneously or intramuscularly separated by a period of at least one week and preferably at least one month. Booster doses are recommended every 6 months to

maintain immunity. When more than 6 months have elapsed since the last dose a single dose is sufficient to boost immunity.

14.3.3 A single dose of vaccine may be sufficient to satisfy the regulations of those countries still requiring proof of cholera vaccination for entry. Cholera vaccine is not recommended for children under one year of age.

14.3.4 The recommended doses for primary and booster immunisation are:

Age	**Deep Subcutaneous/Intramuscular** *Injection*	
	First dose	All subsequent doses
1-5 yrs	0.1 ml	0.3 ml
5-10 yrs	0.3 ml	0.5 ml
Over 10 yrs	0.5 ml	1.0 ml

14.3.5 For booster doses, the vaccine may be administered intradermally in a volume of 0.1 ml for children aged 1-10 years, and 0.2 ml for adults and children over the age of 10 years. This route of administration is recommended to minimise adverse local reactions.

14.4 Side-effects and Adverse Reactions

14.4.1 Cholera vaccination will occasionally cause some local tenderness and redness at the injection site lasting 1-2 days. This may be accompanied by fever, malaise and headache. Serious reactions are extremely rare, but when they do occur, constitute a contra-indication to further doses.

14.5 Contra-indications

14.5.1 It is prudent to avoid administering vaccine to subjects with acute infections or chronic illness. Repeated vaccination

may result in the development of hypersensitivity to constituents of the vaccine. Severe reactions to cholera vaccination constitutes a contra-indication to further doses.

14.5.2 It is very important that any severe reaction following the administration of cholera vaccine, whether or not considered to be due to the vaccine should be reported without delay to the Committee on Safety of Medicines using the yellow card system. Although there is no specific information to suggest that cholera vaccine is unsafe during pregnancy, it should only be used when clear indications exist.

14.6 Management of outbreaks

14.6.1 Cholera vaccine has no role in the management of contacts of imported cases or in controlling the spread of infection. Sources of infections should be identified and suitable measures taken to eradicate them. Contacts should maintain high standards of personal hygiene to avoid becoming infected. Control of the disease is based on permanent public health measures rather than vaccination programmes.

14.7 Supplies

14.7.1 Cholera vaccine (Cho/Vac) contains heat-killed phenol preserved *Vibrio cholerae,* Serovar O1 sub types Inaba and Ogawa, at a concentration of not less than 8000 million organisms per ml. Vials of 1.5 ml and 10 ml are available, manufactured by the Wellcome Foundation Ltd. Tel: Crewe (0270) 583151.

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IMMUNISATION AGAINST INFECTIOUS DISEASE

15. VIRAL HEPATITIS

HEPATITIS B

15.1 Introduction

15.1.1 Viral Hepatitis B usually has an insidious onset with anorexia, vague abdominal discomfort, nausea and vomiting, sometimes arthralgia and rash, which often progresses to jaundice. Fever may be absent or mild. The severity of the disease ranges from inapparent infections, which can only be detected by liver function tests, to fulminating, fatal cases of acute hepatic necrosis. Among cases admitted to hospital the fatality rate is about one per cent. The average incubation period is 60 to 90 days but occasionally can be as long as 6-9 months.

15.1.2 The number of overt cases of hepatitis B identified in England and Wales appears to be low, averaging a little over 1,000 cases a year. Hepatitis B surface antigenaemia (HBsAg) is found in about one per thousand volunteers for blood donation; often such individuals do not give a history of clinical hepatitis. A small proportion of antigen carriers develop chronic hepatitis. Sometimes there is impairment of liver function tests; biopsy findings range from normal to inactive hepatitis, with or without cirrhosis. The prognosis of the liver disease in such individuals is at present uncertain. Over 60 per cent of patients with hepatic cell carcinoma may be associated with antigenaemia. However the incidence of such carcinoma in carriers is not known but is probably very low.

15.1.3 Certain occupational and other groups are known to be at increased risk of infection although in comparison with other countries the incidence of the disease is low in Britain.

15.1.4 There are two types of immunisation product, a vaccine which induces an active immune response and a specific immunoglobulin which provides passive immunity after accidental inoculation or contamination with antigen positive blood.

15.2 Vaccine

15.2.1 Hepatitis B vaccine is a suspension of inactivated, alum adsorbed 22 nm hepatitis B surface antigen (HBsAg) particles that have been purified from human plasma by a combination of ultra centrifugation and biochemical procedures. The product is inactivated by a threefold process; each of these processes has been shown to inactivate hepatitis B virus and representative viruses. Hepatitis B vaccine contains 20 ug/ml of hepatitis B surface antigen protein.

15.2.2 Field trials in the United States have demonstrated that the vaccine is 80 per cent to 95 per cent efficient in preventing infection amongst susceptible persons. Protection against illness was complete for persons who developed antibodies after vaccination but before exposure to infection. The duration of protection and the subsequent need for booster doses is not yet known.

15.2.3 The vaccine should be stored at 2 - 8°C but not frozen. *Freezing destroys the potency of the vaccine.*

15.3 Recommendations

15.3.1 The decision as to whether or not to give this vaccine to a particular individual is a matter for professional decision but in view of the relatively low incidence of hepatitis B, the pressure on health service resources and the cost of the vaccine it is recommended that the vaccine should be reserved for specific individuals within groups known to be at increased risk. It is advised that vaccination should be considered for the following individuals:-

HEALTH CARE PERSONNEL

1. Personnel directly involved over a period of time in patient care in those residential institutions for the mentally handicapped where there is a known high incidence of hepatitis B. (The same priority should be accorded to teaching and training staff in similar circumstances).

2. Personnel directly involved in patient care over a period of time, working in units giving treatment to known carriers of hepatitis B infection.

3. Personnel directly involved in patient care working in haemophilia or other centres regularly performing maintenance treatment of patients with blood or blood products.

4. Laboratory workers regularly exposed to increased risk from infected material.

5. NHS and academic health care personnel on secondment to work in areas of the world where there is a high prevalence of hepatitis B infection, if they are to be directly involved in patient care.

PATIENTS AND FAMILY CONTACTS

1. Patients on first entry into those residential institutions for the mentally handicapped where there is known high incidence of hepatitis B.

2. Renal dialysis patients who are known to be antigen/ antibody negative, who are travelling abroad and who will receive haemodialysis treatment in centres outside the United Kingdom.

3. The spouses or other consorts of carriers of hepatitis B in the following circumstances.

a. If the carrier does not have antibody to hepatitis B e antigen.

b. If the potential vaccinee is neither a carrier of hepatitis B surface antigen nor hepatitis B antibody positive.

15.3.2 The vaccine need not be given to individuals known to be hepatitis B surface antigen (or antibody) positive or to patients with acute hepatitis B since in the former case it would be unnecessary and in the latter ineffective. Intimate contacts of individuals suffering from acute hepatitis B should be treated by passive immunisation (see below).

15.3.3 **Recommended dosage for primary immunisation.**

The immunisation regimen consists of three doses of vaccine by intramuscular injection except in patients with haemophilia in whom the subcutaneous route can be used.

1st dose	at elected date
2nd dose	1 month later
3rd dose	6 months after first dose, as a 'booster'

GROUP	INITIAL	1 MONTH	6 MONTHS
Children 6 months to 10 years	0.5 ml (10 mcg)	0.5 ml (10 mcg)	0.5 ml (10 mcg)
Adults and children over 10 years	1.0 ml (20 mcg)	1.0 ml (20 mcg)	1.0 ml (20 mcg)
Dialysis and immunocompromised	Doses to be determined from ongoing studies		

15.4 **Side-effects and adverse reactions**

15.4.1 Side-effects among 12,000 recipients of hepatitis B vaccine observed to date have been limited to soreness and redness at the injection site. No information is available on the safety of the vaccine for the developing fetus, but because it contains only non-infectious HBsAg particles the risk to the fetus from the vaccine should be negligible. In contrast hepatitis B infection in pregnant women may result in severe disease for the mother and chronic infection for the newborn. Pregnancy should not be considered a contra-indication to the use of this vaccine for persons who are otherwise eligible.

15.4.2 Since this is a new vaccine it is even more important that adverse reactions should be reported to the Committee on Safety of Medicines (by the 'Yellow Card System').

15.5 Effect of vaccination on carriers

15.5.1 The vaccine produces neither therapeutic nor adverse effects on carriers of hepatitis B.

15.6 Contra-indications

15.6.1 Vaccination should be postponed in individuals suffering from serious infections.

15.6.2 Caution should be exercised in administrating hepatitis B vaccine to individuals in whom a febrile or systemic reaction could pose a significant risk.

15.7 Supplies

15.7.1 Hepatitis B vaccine is available from Thomas Morson Pharmaceuticals. **(Tel: Hoddesdon (0992) 445252)**

15.8 Hepatitis B Immunoglobulin

15.8.1 Immunoglobulin is available for the passive immunisation against hepatitis B. It is used for the following circumstances:-

a. Persons who are accidentally inoculated or who contaminate the eye or mouth or fresh cuts or abrasions of skin with blood from a known carrier of HBsAg. Individuals who sustain such accidents should wash the affected area well and seek medical advice. Advice about prophylaxis after such accidents should be obtained by tele-phone from the nearest Public Health Laboratory. Hepatitis B immunoglobulin is held in Scotland by the Blood Transfusion Service. Advice following accidental exposure may be obtained from the Hospital Control of Infection officer or the Community Medicine Specialist (Environmental Health).

b. Children born to mothers who develop acute hepatitis B in the last trimester of pregnancy or who are highly infective HBsAg carriers should be immunised in the neonatal period, beginning as soon as possible after birth but not later than 48 hours.

c. Sexual consorts and, in some circumstances, a family contact judged to be at high risk, of individuals suffering from acute hepatitis B. *Supplies* Public Health Laboratory Service. (Tel 01-205 7041.) Note: Supplies of this product are limited and demands should be restricted to patients in whom there is a clear indication for its use.

15.9 HEPATITIS A

15.9.1 Viral hepatitis A is usually transmitted by the faecal oral route usually after the ingestion of contaminated food or drink. The disease is usually milder than hepatitis B and is very seldom fatal. A chronic carrier state is unknown and chronic liver damage is extremely unlikely. The incubation period is about 30 days. Outbreaks occasionally occur in this country although most cases occur sporadically. Persons travelling to developing countries may be at greater risk of contracting hepatitis A.

15.9.2 Human normal immunoglobulin offers protection against infection with hepatitis A and is normally used under the following circumstances:-

a. to control outbreaks of hepatitis A in households and in institutions,

b. for persons travelling to areas of poor sanitation.

15.9.3 Human normal immunoglobulin may interfere with the development of active immunity from live virus vaccines. It is therefore wise to adminster live virus vaccines at least 3 weeks before the administration of immunoglobulin. If immunoglobulin has been administered first then an interval of 3 months should be observed before administering a live virus vaccine.

15.9.4 **Supplies** The Public Health Laboratory Service. Tel: 01-205 7041.

IMMUNISATION AGAINST INFECTIOUS DISEASE

16. INFLUENZA

16.1 Introduction

16.1.1 Influenza is an acute viral disease of the respiratory tract characterised by the abrupt onset of fever, chills, headache, myalgia and sometimes prostration. Coryza and sore throat are common and a dry cough is almost invariable. It is usually a self-limiting disease with recovery in 2-7 days. There is serological evidence of asymp tomatic infections. Influenza is highly contagious and derives its importance from the rapidity with which epidemics evolve and the seriousness of the complications, notably bacterial pneumonia. These features account for the widespread morbidity affecting all age groups but mortality is mostly confined to the elderly and chronic sick. Mortality, measured by the number of excess deaths attributable to influenza, is in the region of three to four thousand even in winters when the incidence is low.

16.1.2 There are three types of influenza virus: A, B and C. The latter appears to be of lesser importance. Epidemic influenza is usually caused by influenza A which attacks persons in all age-groups but with the highest incidence in children and adolescents. Out-breaks which are confined to children, particularly those in institutions, may be due to either influenza A or B. The latter virus only causes general epidemics at intervals of several years, whereas influenza A epidemics occur in most years. Influenza A viruses are antigenically labile and the principle surface antigens, the haemagglutinin and neuraminidase, undergo antigenic changes. Major changes (so called 'antigenic shifts') occur periodically and are responsible for the emergence of sub-types which may cause pandemics. More minor changes (so called 'antigenic drifts') occur more frequently and are responsible for the interpandemic prevalence of influenza. Marked antigenic drift may be followed by large winter epidemics, but it is rarely possible to forecast the severity of outbreaks. The implications for the production of influenza vaccine are that the vaccine must be altered, sometimes each year, to keep up with and match the antigenic changes of wild virus.

16.2 Vaccine

16.2.1 The antigenic composition of the current virus strains must be considered in selecting the strains to be included in the vaccine. Influenza vaccine formulation is reviewed annually and

when significant alterations in antigen have occurred, changes in the composition are made to counter 'antigenic shifts' and 'antigenic drifts'.

16.2.2 Influenza virus vaccine is available as "whole-virus" vaccine,"split virus" vaccine, and as "surface antigen" vaccine. Each is prepared from virus cultured in embryonated hen's eggs.

a. "Whole-virus" vaccine contains inactivated influenza virus purified by zonal ultra-centrifugation.

b. "Split virus" vaccine is a partially purified influenza vaccine containing disrupted virus particles prepared by treating whole virus particles with organic solvents or detergents and separating by zonal ultra-centrifugation.

c. "Surface antigen" vaccine contains highly purified haemagglutinin and neuraminidase antigens prepared from disrupted virus particles. The antigens may be adsorbed on to aluminium hydroxide.

16.2.3 The vaccines may contain the antigens of only one strain of virus (monovalent) but more commonly are bivalent or trivalent, and contain antigens of the current influenza A and influenza B virus strains. "Surface antigen" vaccines cause fewer adverse reactions in children than "whole-virus" vaccines.

16.2.4 The vaccines should be stored at 2-8°C and be protected from light. The vaccine should be allowed to reach room temperature before being administered by deep subcutaneous or intramuscular injection. Unused contents of multi-dose vials should be discarded at the end of the vaccination session.

16.2.5 Currently available influenza vaccines confer about 70 per cent protection against infection for about a year after administration. Low levels of protection may persist for a further one to two years, if the prevalent strain remains the same or undergoes only minor 'antigenic drift'. In order to provide continual protection annual immunisation is desirable, although the value of annual vaccination in periods of 'antigenic drift' is uncertain.

16.3 Recommendations

16.3.1 Recommendations to doctors on the use of influenza vaccine are issued by the Department of Health and Social Security by a letter from the Chief Medical Officer. The most recent statement should be consulted for details of the recommended composition and dosage of available vaccines.

16.3.2 Vaccination is not recommended for the attempted control of the general spread of influenza. Individual protection with an appropriate inactivated vaccine (see below) should be considered for persons at special risk provided that vaccine is not contra-indicated, (*eg* by known sensitivity to egg products). The groups regarded as being at special risk include persons, especially the elderly, suffering from the following conditions:-

a. chronic pulmonary disease

b. chronic heart disease

c. chronic renal disease

d. diabetes and possibly other less common endocrine disorders

e. conditions in which consideration has to be given to the use of immunosuppressive therapy.

This list is not intended to cover all possible disorders for which immunisation against influenza may be indicated.

f. The vaccine should be considered for elderly persons living in residential homes and long stay hospital accommodation in which rapid spread is likely to follow the introduction of infection. (Over 70 per cent of deaths attributed to influenza occur in persons over 65 years of age.)

g. The vaccine might also be considered for children living in hospitals or residential establishments in which rapid spread is likely to follow the introduction of infection. To minimise the risk of febrile reactions after

influenza vaccine, the Joint Committee now recommend that for children purified surface antigen vaccine be used. The most recent CMO's letter will give a recommended lower age limit for vaccination of children which may vary from year to year as it depends on the evidence of safety and effectiveness provided for each vaccine.

16.3.3 Vaccination of Health Service staff is generally indicated only for those individuals at increased risk owing to medical disorders such as those referred to above. In the event of a pandemic or other major outbreak it may be advisable to vaccinate those staff liable to be heavily exposed to infection; such advice would be specially promulgated at the time.

16.3.4 Whether to vaccinate in any particular case is for the individual doctor to decide. Adverse reactions to influenza vaccine should be reported to the Committee on Safety of Medicines using the yellow card system.

16.4 Side-effects and adverse reactions

16.4.1 Local reactions, consisting of redness and induration at the injection site lasting 1 to 2 days may occur in up to a third of recipients but these are usually mild. Recent influenza virus vaccines have been associated with few side-effects. Three types of systemic reactions have been described:

a. Fever, malaise, myalgia beginning 6-12 hours after vaccination and persisting 1-2 days. This occurs more often in children than adults, and more frequently with whole virus vaccine than surface antigen vaccine.

b. Immediate responses of an allergic nature resulting in urticaria or respiratory expressions of hypersensitivity. These occur extremely rarely.

c. From experience in the USA following widespread administration of swine influenza vaccine, recipients of influenza vaccine may be at increased risk of developing Guillain-Barré Syndrome, a paralytic syndrome that is usually self-limiting and reversible. However, of those affected in 5-10 per cent of cases there is some residual weakness and about 5 per cent of cases prove fatal. Before 1976 no such association was recognised. During

that year, people receiving swine influenza vaccine were shown to be at excess risk of developing this paralytic syndrome. However, analysis of the data for the years since 1976, when vaccines containing the swine influenza component have not been in use, has failed to demonstrate this risk.

16.5 Contra-indications

16.5.1 a. Individuals with hypersensitivity to eggs should not be given influenza vaccine as residual egg protein is present in minute quantities. The vaccine should not be used in persons hypersensitive to polymyxin or neomycin as traces of these antibiotics may be present.

b. *Use in pregnancy*

There is no evidence that influenza vaccine, prepared from inactivated virus, causes damage to the fetus. It would however be prudent, as with other drug preparations in pregnancy, to restrict administration of influenza vaccine to patients where there is an indication for its use. There is some evidence from past pandemic experience which suggests that infection with influenza virus may cause an increased risk of maternal mortality, congenital malformations of the fetus and increased incidence of leukaemia among children born of mothers who have had influenza. Other studies have not supported these observations, thus the significance of influenza during pregnancy is uncertain.

16.6 Management of outbreaks

16.6.1 As transmission of influenza virus is by person-to-person via the respiratory tract, one method of limiting an outbreak is to interrupt the chain of infection. The wearing of face masks has been recommended in some countries but its effectiveness is uncertain. Influenza has a higher mortality in the elderly and chronic sick, and it may be sensible to minimise their contact with infected people during an outbreak. When an outbreak has occurred, it is too late for immunisation to be of benefit to contacts. However, antiviral chemoprophylaxis, such as amantidine hydrochloride, may give protection against influenza A infection.

INFLUENZA

16.7 Supplies

16.7.1 Information on currently available vaccines is contained in the latest CMO letter issued by the Department of Health and Social Security.

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IMMUNISATION AGAINST INFECTIOUS DISEASE

17. RABIES

17.1 Introduction

17.1.1 Rabies is an acute viral infection resulting in encephalomyelitis. The onset is insidious. Early symptoms are non-specific but may include abnormal sensation around the site of the wound, fever, headache and malaise. The disease may develop in one of two forms. In one, the manifestations include hydrophobia, hallucinations, and maniacal behaviour progressing to paralysis and coma. In the other it develops with signs of an ascending flaccid paralysis and sensory disturbance. It is almost invariably fatal, death resulting from respiratory paralysis. The incubation period is generally 2-8 weeks, but may range from 9 days to two years.

17.1.2 Although the usual mode of infection is via the bite of a rabid animal, transmission of the virus can also occur through mucous membranes, though not, as far as is known, through intact skin. Person-to-person spread of the disease is extremely rare, but recent instances of transmission by corneal graft have been reported. No case of indigenous human rabies has been reported in the United Kingdom since 1902 although cases occur in persons infected abroad. The disease occurs in all continents except Australasia and Antarctica. Rabies in animals has spread throughout a great part of Central and Western Europe since 1945 and continues to advance westwards. The leading infected species in Europe has been the fox, though many other animals may become infected - these include domesticated dogs and cats; cattle, horses, badgers, martens and deer. For United Kingdom residents, prevention of human rabies involves the control of imported animals and the use of pre-exposure vaccine in high-risk individuals. Pre-exposure use of rabies vaccine also should be considered for persons travelling to high risk areas who are likely to be exposed to rabies and who may have difficulty in obtaining prompt post-exposure treatment. Rabies vaccination is also used in the post-exposure management of individuals who may have been infected.

17.1.3 There are two types of immunising products - vaccines that induce an active immune response and immunoglobulin which provides passive immunity. Vaccine is used for pre-exposure protection, whilst both vaccine and immunoglobulin may be needed for rabies post-exposure treatment.

17.2 Vaccine

17.2.1 The vaccine currently available is a human diploid cell vaccine (HDCV). It is a freeze-dried suspension of Wistar rabies virus strain PM/WI 38 1503-3M cultured on human diploid cells and inactivated by beta-propiolactone. For post-exposure treatment the potency of the reconstituted vaccine should be not less than 2.5 x the International Standard per 1 ml dose. The freeze dried vaccine should be stored at 4°C and used immediately after re-constitution with the diluent supplied. It may be administered by deep subcutaneous, intramuscular or intradermal injection. Trials indicate that this vaccine provides a strong antigenic stimulus and will induce antibody formation in most recipients though antibody may not be apparent until the tenth day of a course.

17.2.2 If for any reason HDCV is not available, duck embryo vaccine (DEV) may be used for post-exposure treatment. It is administered by deep subcutaneous injections.

17.3 Recommendations

17.3.1 Rabies vaccine may be used for pre-exposure prophylaxis and post-exposure treatment (see under Management of Cases). Preexposure vaccination is a recognised precaution for persons at special risk of contracting rabies and, in particular, should be offered to those who are employed:

a. at animal quarantine premises for imported animals and zoological establishments

b. as carrying agents authorised to carry imported animals

c. at approved research and acclimatisation centres where primates and other imported animals are housed

d. at national ports of entry where contact with imported animals is likely (eg Customs and Excise Officers)

e. as veterinary and technical staff of the Ministry of Agriculture, Fisheries and Food (MAFF) and Department of Agriculture and Fisheries for Scotland (DAFS)

f. as inspectors appointed by local authorities under the Diseases of Animals Act or employed otherwise who, by reason of their employment, encounter enhanced risk

g. in laboratories handling rabies virus

h. as health workers who come into close contact with a patient with rabies

i. as workers in enzootic areas where they may be at special risk (eg veterinary staff or persons working in remote areas in developing countries). It is *not* recommended as a *routine* prophylactic measure for travellers going abroad.

17.3.2 For pre-exposure protection two doses of vaccine each of 1.0 ml should be given four weeks apart by deep subcutaneous or intramuscular injection. A reinforcing dose is given after 12 months and additional reinforcing doses given every one-three years depending on the risk of exposure. Alternatively when more than one person is to be vaccinated the vaccine may be administered in smaller doses (0.1 ml) by the intradermal route with the same time intervals as above. It is emphasised that intradermal vaccination is reliable only if the whole of the 0.1 ml dose is properly given into the dermis. For those not experienced in the technique, the use of a full dose intramuscularly is advised. Staff who are engaged in the care of a patient with rabies may be rapidly immunised by receiving 0.1 ml of vaccine intradermally in each limb (0.4 ml in all) on the first day of exposure to the patient.

17.3.3 Many health authorities recommend that a serological test should be carried out on all people receiving rabies vaccine for pre-exposure immunisation, to ensure that they are adequately protected.

17.4 Side-effects and adverse reactions

17.4.1 Human diploid cell vaccine may cause local reactions such as redness, swelling or pain at the site of injection occurring within 24-48 hours of administration. Systemic reactions such as headache, fever, muscle aches and vomiting have been reported occurring within 24 hours, also urticarial rashes. Anaphylactic shock has been reported in the USA and Guillain-Barre syndrome in Norway following administration of HDC vaccine.

17.4.2 Duck embryo vaccine commonly causes local reactions. Most recipients experience pain, erythema and induration at the injection site. Systemic reactions occur in a third of patients. Anaphylaxis may occur and rarely neuroparalytic reactions have been reported. Fatal reactions are estimated to occur in about 1 per 33,000 vaccinations.

17.4.3 Adverse reactions should be reported to the Committee on Safety of Medicines using the Yellow Card system.

17.5 Contra-indications

17.5.1 There are no specific contra-indications to human diploid cell vaccine (HDCV), though if there was evidence of hypersensitivity to the vaccine then discontinuation of pre-exposure vaccination would be advisable.

17.5.2 It may be prudent to delay pre-exposure vaccination of pregnant women, though if the risk of exposure to rabies is high, then vaccine should be given.

17.6 Management of cases

17.6.1 Should an outbreak in animals occur, and a rabies-infected area be declared, vaccination would need to be offered, as appropriate, to those persons directly involved in control measures and to veterinary surgeons engaged in private practice within the infected area and their ancillary staff.

17.6.2 Human rabies is a notifiable disease. In the event of a case of human rabies, the Medical Officer for Environmental Health or in Scotland the Chief Administrative Medical Officer should be informed. Detailed advice on the management of an outbreak appears in the "Memorandum on Rabies" issued by the DHSS in 1977, and this should be referred to. Scottish arrangements are detailed in the SHHD Memorandum on Rabies of 1977.

17.6.3 The treatment of persons with a history of exposure, *ie* a bite, a scratch or an abrasion by an animal suspected or known to be suffering from rabies should be started as soon as possible after exposure and should consist of both local and systemic approaches using active and passive immunisation.

17.6.4 *Human diploid cell vaccine* is the vaccine of choice. 1ml of vaccine should be given by deep subcutaneous or intramuscular injection on days 0, 3, 7, 14, 30 and 90. (Day 0 is the day the patient receives the first dose.)

17.6.5 Passive immunisation with *human rabies immunoglobulin (HRIG)* provides rapid immune protection for a short period and can be used in combination with HDCV in post-exposure treatment to cover the delay associated with active immunisation. Human rabies immunoglobulin is obtained from the plasma of vaccinated human donors. Its content is standardised to 150 iu per ml and dosage is dependent on body weight. Up to half the dose should be thoroughly infiltrated in the area of the wound, and the rest administered intramuscularly. No more than the recommended dose should be given. A total dose of 20 iu per Kg body weight should be administered. Local pain and low grade fever may follow receipt of rabies immunoglobulin, but no serious adverse reactions have been reported.

a. **Local treatment**

Thorough cleansing of the wound.

Instillation and infiltration of human rabies immunoglobulin in and around the wound.

Tetanus prophylaxis and antibiotics should be given as required.

b. **Special systemic treatment**

Passive immunisation with human rabies immunoglobulin.

Active immunisation with rabies vaccine.

17.6.6 The following is a simple guide to post-exposure vaccination.

RABIES

Nature of exposure		Status of biting animal irrespective of previous vaccination		Recommended treatment
		At time of exposure	During 10 days[a]	
I	Contact, but no lesions; indirect contact; no contact.	Rabid		None
II	Licks of the skin; scratches or abrasions; minor bites (covered areas of arms, trunk and legs).	(a) Suspected as rabid[b]	Healthy	Start vaccine. Stop treatment if animal remains healthy for 5 days[a,c].
			Rabid	Start vaccine; administer HRIG upon positive diagnosis and complete the course of vaccine.
		(b) Rabid; wild animal[d], or animal unavailable for observation.		HRIG + vaccine.
III	Licks of mucosa: major bites (multiple or on face, head, finger, or neck).	Suspect[b] or rabid domestic or wild[d] animal, or animal unavailable for observation.		HRIG + vaccine. Stop treatment if animal remains healthy for 5 days[a,c].

a. Observation period in this chart applies only to dogs and cats.

b. All unprovoked bites in endemic areas should be considered suspect unless proved negative by laboratory examination (brain FA).

c. Or if its brain is found negative by fluorescent antibody examination.

d. In general, exposure to rodents and rabbits seldom, if ever, requires specific antirabies treatment.

17.6.7 If human diploid cell vaccine is not available, duck embryo vaccine (DEV) may be used. It should be administered by deep subcutaneous injection daily for 14 days, if given without passive immunisation or for 21 days if given with immunoglobulin. This should be followed by booster doses 10,20 and 90 days after the final primary course dose. Duck embryo vaccine (DEV) should not be given to persons allergic to eggs, particularly duck eggs.

17.6.8 In the case of travellers returning to this country who report an exposure to an animal abroad it may often be advisable to start treatment while enquiries are made on the presence of rabies in the country concerned, and where possible, the health of the biting animal. In this connection the Communicable Disease Surveillance Centre, London (01-200 6868) or for Scotland, the Communicable Diseases (Scotland) Unit (041-946 7120), may be able to provide the necessary information.

17.6.9 For a person who has received a full pre-exposure course of vaccine and been shown to have developed serum antibody, a modified course of post-exposure vaccine may be given following a bite by a possible rabid animal. Advice on this subject should be obtained from the Virus Reference Laboratory, Central Public Health Laboratory, Colindale, London (01-205 7041).

17.7 Supplies

17.7.1 a. Human diploid cell vaccine (HDCV) is a lyophilised, suspension of inactivated Wistar rabies virus strain PM/WI 38 1503-3M. It is cultured on human diploid cells and inactivated by beta-propiolactone. Potency is not less than 2.5 x the International Standard per 1 ml dose.

Manufactured by Institut Merieux, France.

HDCV for persons in categories 17.3.1. a-h (see Recommendations) is supplied by the DHSS and available from the Public Health Laboratories at Birmingham, Cardiff, Exeter, Leeds, Liverpool, London (Colindale) and Newcastle. For persons in category 17.3.1.i it should be obtained from commercial sources; Servier Laboratories Limited. (Phone Fulmer (02816) 2744).

b. Human rabies immunoglobulin (HRIG) is antirabies gammaglobulin concentrated from plasma of immunised human donors. It contains 150 iu per ml.

Manufactured by Blood Products Laboratory and supplied through certain Public Health Laboratories listed in "Memorandum on Rabies" issued by the DHSS 1977.

c. Supply Centres in Scotland for HDCV and HRIG are listed in the SHHD Memorandum on Rabies.

d. Rabies duck embryo vaccine (DEV) is a lyophilised vaccine prepared from virus cultured on embroyonated duck eggs and inactivated with beta-propiolactone.

Manufactured by Eli Lilly and Co. Ltd, Basingstoke. (Tel: 0256 3241.)

IMMUNISATION AGAINST INFECTIOUS DISEASE

18. YELLOW FEVER

18.1 Introduction

18.1.1 Yellow fever is an acute viral infection occurring in the tropics of Africa and South America; it has never occurred in Asia. It ranges in severity from a clinically indeterminate condition to an illness of sudden onset with fever, vomiting and prostration which may progress with haemorrhagic symptoms and jaundice. In indigenous populations in endemic areas, fatality is about 5 per cent, whereas in non-indigenous individuals or during epidemics the fatality rate may be as high as 50 per cent. Two forms of the disease are distinguishable epidemiologically - urban and jungle - though clinically and aetiologically they are identical. Only a few outbreaks of urban yellow fever have occurred in recent years. The incubation period is 2-5 days.

18.1.2 Urban yellow fever is spread from infected to susceptible persons by the *Aedes aegypti* mosquito, a mosquito tending to live and breed in close association with man. Jungle yellow fever is a zoonosis transmitted among non-human hosts (mainly monkeys) by forest mosquitoes which may also bite and infect humans. Such infected humans may if subsequently bitten by *Aedes aegypti* mosquitoes become the source of outbreaks of the urban form of the disease.

18.1.3 Preventive measures against urban yellow fever include eradication of Aedes mosquitoes, protection from mosquito bites and vaccination. Jungle yellow fever can only be prevented in humans by vaccination.

18.2 Vaccine

18.2.1 Yellow fever vaccine (Yel/Vac) is a live attenuated freeze dried preparation of the 17D strain of yellow fever virus. Each 0.5ml dose contains not less than 1,000 mouse LD_{50} units. It is propagated in leucosis-free chick embryos and contains no more than 2 i.u. of neomycin and 5 i.u. of polymyxin.

18.2.2 It should be stored below 8°C, protected from light. The diluent, sterile water specially tested to ensure that it does not inhibit the vaccine virus, should be stored upright in a cool place (below 15°C), but not frozen. The vaccine should be administered by deep subcutaneous injection within one hour of reconstitution.

18.2.3 A single dose correctly administered confers immunity in almost 100 per cent of recipients. Immunity persists for at least 10 years and may be for life.

18.3 Recommendations

18.3.1 It is recommended that the following persons should be vaccinated:-

a. Laboratory workers handling infected material.

b. Persons, nine months of age or older, travelling through or living in infected areas.

c. Travellers entering yellow fever receptive areas from infected areas may require evidence of having been vaccinated - a valid International Certificate of Vaccination. These requirements change, so all travellers should seek current information from the relevant Embassy, Mission or one of the Health Departments.

18.3.2 The dose is 0.5ml irrespective of the age of the recipients. Primary vaccination is valid from the 10th day after vaccination as regards the International Certificate. For the purposes of international travel, yellow fever vaccine is only administered at Yellow Fever Vaccination Centres approved by WHO. A list of such centres in the United Kingdom appears in the most recent edition of "Protect your health abroad" DHSS SA35.

18.3.3 Revaccination every 10 years is required for purposes of international travel and is recommended for laboratory workers at special risk.

18.4 Side-effects and adverse reactions

18.4.1 Severe reactions to the vaccine are extremely rare. Five to ten per cent of recipients have mild headache, myalgia, low grade fever, or soreness at the site of injection, 5-10 days after vaccination. Fewer than 0.2 per cent have to restrict their regular activities.

18.4.2 The only serious reactions following administration of the 17D tissue culture vaccine has been the rare occurrence of encephalitis in young infants. All have recovered without sequelae. Vaccination of infants under the age of 9 months is therefore not recommended and they should not be exposed to yellow fever.

18.4.3 Severe reactions observed following immunisation with yellow fever vaccine should be reported to the Committee on Safety of Medicines using the yellow card system.

18.5 Contra-indications

18.5.1 Yellow fever vaccine is a live virus vaccine and the contra-indication to these vaccines should be observed. Vaccination should be avoided in:-

i. persons suffering from febrile illness;

ii. patients receiving corticosteroid or immunosuppressive treatment, including general irradiation;

iii. patients suffering from malignant conditions such as lymphoma, leukaemia, Hodgkin's disease or other tumours of the reticuloendothelial system or where the normal immunological mechanism may be impaired, as for example in hypogammaglobulinaemia;

iv. pregnant women because of the theoretical risk of fetal infection. However if a pregnant woman must travel to areas where the risk of yellow fever is high, she should be vaccinated as the small theoretical risk of vaccination is far outweighed by the risk from yellow fever infection.

18.5.2 With persons in whom it is necessary to administer more than one live virus vaccine, the vaccines should be given simultaneously at different sites, or separated by an interval of at least 3 weeks.

18.5.3 In addition, infants below the age of 9 months should not be vaccinated since the small number of cases of encephalitis that have been reported have nearly all occurred in infants under this age. However, as with pregnant women, if the risk of infection with yellow fever is high, then vaccination should be performed.

18.5.4 Since the vaccine contains traces of neomycin and polymyxin, it should not be administered to persons known to be hypersensitive to these antibiotics. Vaccination should also be avoided in persons hypersensitive to egg or chick protein. For such persons, a document stating that vaccination is

contra-indicated may be acceptable to some governments. Advice should be sought from that country's Embassy or Mission.

18.6 Management of outbreaks

18.6.1 The vector mosquito does not occur in the United Kingdom and therefore there is no risk of transmission from imported cases.

18.7 Supplies

18.7.1 Yellow fever vaccine (Yel/Vac) is a specially stabilised freeze-dried preparation of the living attenuated 17D strain of yellow fever virus, containing not less than 1000 mouse LD_{50} units in 0.5ml. Traces of neomycin and polymyxin are present. The diluent consists of sterile water specially tested to ensure that it does not inhibit the vaccine virus.

18.7.2 Manufacted by the Wellcome Foundation Ltd. Tel: Crew Crewe (0270) 583151.

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IMMUNISATION AGAINST INFECTIOUS DISEASE

19. TYPHOID FEVER

19.1 Introduction

19.1.1 Typhoid and paratyphoid fevers are generalised enteric infections caused by bacteria of the *Salmonella* species. This group of infective agents comprises over 1000 serotypes, most of which do not give rise to systemic invasion and at most cause only gastro-enteritis or "food poisoning". However, *S. typhi, S. paratyphi A, B and C* and occasionally other *Salmonella* species may produce systemic infection with prolonged pyrexia, prostration and the characteristic clinical picture of 'enteric' fever. The incubation period, which depends on the size of the infecting dose, is usually one to three weeks. Whilst all cases discharge bacilli during their illness, about 10 per cent continue to excrete for three months and two to five per cent become permanent carriers - the likelihood of becoming a chronic carrier increasing with age.

19.1.2 *Salmonella typhi* is usually transmitted by food and drink that has been contaminated with excreta of a human case or carrier. Person-to-person spread is relatively unimportant. Recent examples of sources of outbreaks include canned corned beef (Aberdeen 1964), water supplies (Zermatt 1963) and shellfish contaminated by infected water or sewage. Typhoid is now predominantly a disease of countries where water or food supplies are liable to faecal contamination. In 1938 there were nearly 1000 notifications and 144 deaths in England and Wales attributable to typhoid but by 1960 the incidence had declined to under 100 notifications with three deaths. However, between 1967 and 1979 the annual number of notifications rose from about 150 to 250. In addition, since 1973 the proportion of infections acquired abroad, principally in the Indian sub-continent, has steadily increased from about 60 per cent to 90 per cent.

19.1.3 Combined typhoid and paratyphoid A and B vaccine is no longer available, there is therefore no currently available vaccine for protecting against paratyphoid fever.

19.2 Monovalent Typhoid Vaccine

19.2.1 Immunisation against typhoid fever may be achieved using a vaccine containing killed *Salmonella typhi* (Typhoid/vac). Controlled field trials have demonstrated that typhoid vaccine

confers a useful degree of immunity (about 70-90 per cent) which falls off after one year if one dose is administered, but may last up to three years or longer when two doses are given. The effectiveness of the protection conferred appears to depend on the size of the infecting dose subsequently encountered.

19.2.2 The combined typhoid/paratyphoid A and B (TAB) vaccine, used in the past could cause more severe reactions than the plain typhoid vaccine and because the protective effect of the combined vaccine against paratyphoid A and B fevers was uncertain, use of TAB was discontinued and now only monovalent typhoid vaccine is used.

19.2.3 Typhoid vaccine may be administered by deep subcutaneous, intramuscular or intradermal injections, though the intradermal route, using a reduced dose of vaccine, is not advised for the first dose. There appear to be fewer systemic adverse reactions associated with intradermal administration. However, whilst there is serological evidence of the effectiveness of intradermal injection, this method of administration has not been proven in controlled field trials.

19.2.4 The vaccine should be stored at 2-8°C. Any partly used multi-dose containers should be discarded at the end of the vaccination session.

19.3 Recommendations

19.3.1 Routine typhoid vaccination is not recommended, however administration of monovalent typhoid vaccine (Typhoid/Vac) should be considered in the following persons:-

i. All persons travelling abroad with the exception of those going to Canada, USA, Australia, New Zealand and Northern Europe.

ii. Laboratory workers handling specimens or materials that may contain typhoid organisms.

iii. Persons with intimate exposure to a known typhoid carrier such as would occur with continued household contact.

19.3.2 The basic course of vaccination consists of two doses separated by 4-6 weeks.

a. **Adults and children over 10 years**

	Deep subcutaneous/intramuscular	Intradermal
Basic 1	0.5 ml	
2	0.5 ml	0.1 ml
Reinforcement	0.5 ml (every 3 years)	0.1 ml

b. **Children 1 to 10 years**

	Deep subcutaneous/intramuscular	Intradermal
Basic 1	0.25 ml	
2	0.25 ml	0.1 ml
Reinforcement	0.25 ml (every 3 years)	0.1 ml

19.3.3 Deep subcutaneous or intramuscular injection should be used for the first dose. Although two doses of vaccine are recommended for primary immunisation, one dose is almost as effective for a short period. Typhoid vaccine is not recommended for infants under one year as the risk of infection in infants is low. Under conditions of continued or repeated exposure to infection, a reinforcing dose of vaccine should be administered every three years. When more than three years have elapsed since the last dose, a single dose is sufficient to boost immunity.

19.4 Side-effects and adverse reactions

19.4.1 Typhoid vaccine commonly produces local reactions. Local redness, swelling, pain and tenderness may appear after two or three hours and persist for a few days. In some individuals systemic reactions occur, such as malaise, nausea, headache or pyrexia but usually disappear within 36 hours. Systemic reactions involving neurological complications have been described but are rare. Reactions are especially common in persons who have had repeated injections of typhoid vaccine, and are often more marked in persons over the age of 35 years. Systemic reactions are reduced when the intradermal route is employed. Adverse reactions should be reported to the Committee on Safety of Medicines using the Yellow Card system.

19.5 Contra-indcations

19.5.1 a. Vaccination of children under 1 year of age is not advised because of the risk of adverse reactions, the relatively low incidence of typhoid in this age group and the relatively mild course of the disease in infants.

b. Typhoid vaccine should not be given to subjects with acute infections or chronic illnesses.

c. Typhoid vaccine is not recommended in the face of an outbreak of typhoid fever in the UK as no immediate protection is afforded by the vaccine. There is also some possibility of temporarily increasing susceptibility to infection. Moreover the vaccine renders the diagnosis of suspected illness more difficult because of interference with serological tests.

d. Adults who have received a series of regular reinforcing injections of typhoid vaccine have probably developed some degree of basic immunity and repeated doses of typhoid vaccine could lead to hypersensitivity. Re-vaccination of fully immunised adults should only be required in special circumstances and not as a routine.

e. Although there is no specific information to suggest that typhoid vaccine is unsafe during pregnancy, it should only be used when clear indications exist.

19.6 Management of outbreaks

19.6.1 It is important that the Medical Officer for Environmental Health (MOEH) or Chief Administrative Medical Officer (CAMO) should be informed immediately whenever a patient is suspected of suffering from typhoid. There should be no delay in waiting for laboratory confirmation.

19.6.2 Early identification of the source of infection may be vital in limiting spread of the disease. The contacts of patients with enteric fever should be excluded from work if they are involved in food handling. Otherwise no hard and fast rules can be made beyond advice on personal hygiene. There is no role for typhoid vaccine in the control of outbreaks of typhoid fever, as it affords no immediate protection.

19.7 Supplies

19.7.1 Typhoid (monovalent) vaccine (Typhoid/Vac) contains heat-killed, phenol-preserved, Salmonella typhi organisms at a concentration of not less than 1000 million organisms per ml. Vials of 1.5 ml requiring storage at 2-8°C. Manufactured by the Wellcome Foundation Ltd. Tel: Crewe (0276) 583151.

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IMMUNISATION AGAINST INFECTIOUS DISEASE

20. SMALLPOX

20.1 In December 1979, the Global Commission for the Certification of Smallpox Eradication declared the world free of smallpox and this declaration was ratified by the World Health Assembly on 8 May 1980. The United Kingdom endorsed the validity of this declaration and signed the instrument of ratification at the World Health Assembly. In the light of these events, the Health Departments are reviewing their arrangements for handling smallpox or suspected smallpox. The Joint Committee on Vaccination and Immunisation has reviewed the present advice on vaccination against smallpox of which the most recent is contained in the CMO/CNO letter of 13 March 1979 (CMO 79/3, CNO 79/1) and SHHD/CAMO (80)13 of 27 August 1980.

20.2 Since it is most unlikely that there will be any further case of smallpox in this country, the Joint Committee has recommended that vaccination against smallpox should now only be provided for the following groups:-

1. Investigators and staff working on or associated with smallpox and other orthopox viruses.

2. Staff who have agreed to man any hospital which will be designated to deal with patients strongly suspected of having smallpox.

20.3 Vaccination should also be offered, after the possible risks of the procedure have been explained, to:-

a. families of those included in 1 and 2 above;

b. those engaged in the manufacture of the vaccine or who perform vaccination. In order to avoid the additional risk of primary vaccination, previously vaccinated individuals should be employed for these purposes as far as possible.

20.4 Health Service Staff who come into contact with a patient suspected of having smallpox can, like other contacts, be vaccinated after exposure.

20.5 The World Health Organisation has advised that vaccination is no longer needed for international travellers.

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20.6 Doctors are reminded that there is no necessity for vaccination of travellers and that the procedure carries a recognised hazard.

20.7 Severe reactions observed following immunisation with smallpox vaccine should be reported to the Committee on Safety of Medicines using the yellow card system.

20.8 In the event of individuals requiring vaccination, it must be remembered that elective vaccination is contra-indicated when there has been recent exposure to other infections, constitutional upsets, septic conditions, *a history of or the presence of eczema, pregnancy, hypogammaglobulinaemia and/or other immunodeficient disorders, such as leukaemia, lymphoma and reticuloendothelial malignancies.*

20.9 There are no contra-indications to vaccination of contacts of a case of smallpox and in such circumstances persons suffering from eczema and other contra-indications should be vaccinated and given human antivaccinial immunoglobulin into a different limb. (This immunoglobulin is obtainable from the Central Public Health Laboratory at Colindale, and certain other Centres and the Regional Blood Transfusion Centres in Scotland.)

AMENDMENTS TO THIS MEMORANDUM WILL BE ISSUED PERIODICALLY TO RECIPIENTS OF FREE COPIES.

COPIES OF THE AMENDMENTS WILL ALSO BE AVAILABLE FROM THE DHSS LEAFLETS UNIT, PO BOX 21, STANMORE, MIDDLESEX HA7 1AY

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Amendments should be made immediately they are received and should be recorded below

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