

From the Chief
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the Chief
Nursing Officer,
and the Chief
Pharmaceutical
Officer

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PL/CMO/2001/1, PL/CNO/2001/1,
PL/CPHO/2001/1

For action

- District Directors of Public Health
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- Consultants in Communicable Disease Control
- Medical Directors of NHS Trusts
- Chairs of Primary Care Groups
- General Practitioners
- Nurse Executive Directors
- HA Nurse Advisors
- Community Services Pharmacists

For information

Regional Directors
Regional Directors of Public Health
Regional Pharmaceutical Advisors
Chief Executives of HAs
Chief Executives of NHS Trusts
Regional Nurse Directors
Infection Control Doctors
All Pharmacists

9th March 2001

CURRENT VACCINE AND IMMUNISATION ISSUES

This letter is to update you on several important immunisation issues, namely:

1. The latest concerns about MMR vaccine;
2. The Meningitis C immunisation programme;
3. Meningococcal immunisation for asplenic patients;
4. Meningococcal immunisation for pilgrims travelling to Saudi Arabia;
5. Influenza immunisation;
6. Anaphylaxis management.

1. MMR VACCINE

The latest concerns

1.1 Colleagues will be aware of renewed media interest in MMR and of the continuing concerns of some parents about the safety of the vaccine. This has arisen because of publicity given to an article by Drs Andrew Wakefield and Scott Montgomery before and after its publication ('Through a glass, darkly', Adverse Drug Reactions and Toxicological Reviews⁽¹⁾). Dr Wakefield has been in the forefront of suggesting a link between MMR vaccine and long term health problems, especially inflammatory bowel disease (IBD) and autism. Media interest has also focussed on the use of single antigen vaccines as opposed to the recommended combined vaccine.

1.2 *We should like to emphasise the following points:*

- A review of Wakefield and Montgomery's paper by the Medicines Control Agency identified that it contains no new data relevant to the safety of MMR vaccine, that its analyses are incorrect and that it has failed to mention other published work that does not support the views put forward. A detailed critique can be found at www.doh.gov.uk/mmrresponse.htm.
- The Government's independent expert committees, the Committee on Safety of Medicines (CSM) and the Joint Committee on Vaccination and Immunisation (JCVI), have both reviewed a draft of the paper and advised that "MMR vaccine is very safe".⁽²⁾

- The suggested link between MMR and inflammatory bowel disease and autism has been thoroughly investigated. In the light of Dr Wakefield's article, the CSM conducted a further detailed review of the information available at the times of MMR licensing from 1972 onwards and the subsequent safety data on MMR vaccine.
- The view of both the CSM and the JCVI remains that, on the scientific evidence available, there is no causal link between MMR vaccine, autism and bowel disease. This view is supported by expert groups convened by the Medical Research Council; and is the view of the World Health Organisation (WHO).
- The British Medical Association, the Royal College of General Practitioners, Royal College of Paediatrics and Child Health, Royal College of Nursing and the Community Practitioners and Health Visitors Association issued the following joint statement on 12 January: "We welcome this positive statement from the Chairs of these expert committees about MMR vaccine. MMR is a safe and effective vaccine. By contrast, there is a real concern about having the vaccines separately, since children would be left unnecessarily at risk from these potentially serious diseases. **We strongly recommend that children are protected with MMR**".⁽³⁾
- The overwhelming evidence from worldwide experience is that MMR remains the safest way to protect children against these three potentially serious diseases. The WHO said on 24 January 2001: "WHO strongly supports the use of MMR vaccine on the grounds of its convincing record of safety and efficacy".
- There has been no new research that changes our previous advice: ***Children should not be given separate measles, mumps and rubella vaccines in place of MMR, since there is no evidence of benefit and a clear risk of harm from such a practice.***
- We are aware that it has been suggested that the administration of licensed single rubella vaccine to children will allow a practitioner to justify the importation of unlicensed measles and mumps vaccines. 'Immunisation against infectious disease'⁽⁶⁾ advises that rubella vaccine should be used for the protection of seronegative women, and that children, of whatever age up to school-leaving, should be immunised with MMR vaccine.

Information

1.3 We want to ensure that all have access to the best factually accurate scientific information.

Current Vaccine and Immunisation Issues

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This letter is also available on the Internet at:
<http://www.doh.gov.uk/cmo/cmoh.htm>

To meet this need the Department is – following a meeting with various health organisations on 22 January – looking once again at its MMR information resources for both the public and health professionals with the aim of updating those materials. This will involve:

- An information programme to provide factually accurate scientific information to parents and health professionals;
- The preparation of revised leaflets and Factsheets; these will be published as soon as possible and sent to you direct and also be available through health promotion units;
- The provision of posters and a media information campaign;
- A seminar programme to provide information to health professionals.

1.4 In the meantime, Annex 1 to this letter contains responses to some of the questions most frequently asked by parents which we hope you find helpful. **We would encourage all involved in delivering primary care immunisations to familiarise themselves with both the existing comprehensive guidance from the Department and also the revised material when it becomes available.** Detailed information is already on the NHS Health Promotion England immunisation website: www.immunisation.org.uk. This website will be regularly updated as new material becomes available.

2. THE MENINGITIS C IMMUNISATION PROGRAMME

2.1 You will be aware that in November 1999 we initiated a major public health programme to offer the new meningococcal C conjugate (MenC) vaccine to everyone under the age of 18 years⁽⁴⁾. We have recently been able to announce the great success of this programme and the impact which the new vaccine has had on this devastating disease⁽⁵⁾.

2.2 Before the introduction of the vaccine, meningococcal Group C caused an estimated 1,530 cases of meningitis and/or septicaemia with 150 deaths in 1998, mainly in young children and teenagers. In the last six months of 2000 the vaccine reduced meningococcal C disease across all under 18s by 71% (this will have included many children still to be immunised as the programme rolled out), compared with the same period of 1999. In the first groups to be immunised, disease has been reduced by 90% (in 15-17 year olds) and 82% (in under 1s).

2.3 We would like to take this opportunity to formally thank and congratulate everyone involved in delivering this programme; and especially doctors, practice nurses, school nurses, community nurses, health visitors, pharmacists and teachers. Implementing this important initiative involved much hard work and commitment from many people in the health and education sectors. The programme has been a wonderful achievement for the NHS. The UK took a leading role in developing the vaccine and is the first country to introduce it. Babies and young people are alive and well today who would otherwise have died.

Item of Service fee

2.4 **We would encourage all practices to review their patient lists to ensure, in collaboration with the local immunisation co-ordinator, any children or young people missed during the school campaigns are offered the chance through primary care to be protected against this devastating disease. An Item of Service Fee (rate B) is now available for GPs giving the vaccine to anyone under 18 years of age. It is particularly important that we offer vaccine to anyone who was missed in last year's campaign.**

2.5 We would also like to remind colleagues to remain alert to the signs and symptoms of meningococcal disease. The MenC vaccine does not protect against meningococcal B disease (now responsible for almost all childhood cases) and not all individuals have been immunised with the new vaccine.

3. MENINGOCOCCAL IMMUNISATION FOR ASPLENIC PATIENTS

Meningococcal C conjugate vaccine is now recommended for people with an absent or dysfunctional spleen.

3.1 Patients with an absent or dysfunctional spleen (through operative splenectomy, functional hyposplenism or congenital aplasia) are at increased risk of overwhelming bacterial infection. Infection is most commonly pneumococcal, but other organisms such as *Haemophilus influenzae type b* and meningococci may be implicated.

3.2 In addition to the routinely recommended vaccines, immunisation with pneumococcal, Hib and influenza vaccines is currently recommended for hyposplenic individuals⁽⁶⁾. Up to now, meningococcal immunisation (with meningococcal A&C vaccine) was recommended only in high risk situations, such as travel to a high risk area, on the grounds that most infections in the UK were due to group B strains and any protection from the polysaccharide A&C vaccine was likely to be of short duration⁽⁷⁾. **In view of the better efficacy and longer duration of immunity likely to be conferred by conjugate meningococcal C (MenC) vaccine, the JCVI now recommends that MenC vaccine is offered to all patients with an absent or dysfunctional spleen.**

3.3 **When travelling to a high risk area for meningococcal infection, such patients will still require the additional protection conferred by polysaccharide A&C or quadrivalent (A,C,W,Y) vaccine.**

4. IMMUNISATION FOR PILGRIMS TRAVELLING TO SAUDI ARABIA FOR HAJJ OR UMRAH

4.1 Saudi Arabia requires pilgrims entering the country for Hajj or Umrah to be immunised against meningococcal A infection. Previously the UK has recommended meningococcal polysaccharide A&C vaccine. Following a recommendation from the JCVI, this advice has now changed.

4.2 Last year, an outbreak of meningococcal W135 infection was associated with the Hajj⁽⁸⁾. Up to 7 November 2000, 49 cases with the infection had been reported to the Public Health Laboratory Service and 7 people had died. The UK Health Departments therefore now recommend that the quadrivalent meningococcal polysaccharide vaccine, which provides protection against A, C, W135 and Y strains, is more appropriate.

4.3 One licensed product, 'ACWY Vax' (SmithKline Beecham), is available. Details on this are contained in Annex 2 to this letter. **The vaccine should not be used in infants of less than two months. When issuing a certificate of meningococcal immunisation, doctors should indicate which vaccine has been given.**

4.4 Most children and young people up to the age of 18 years in Britain will now have been immunised with MenC vaccine, either by their GP or in school. MenC vaccine protects only against meningococcal C infection. Children and young people travelling for Hajj or Umrah will still need the additional protection against A and W135 strains afforded by the quadrivalent vaccine. An interval of at least two weeks is recommended before administering the quadrivalent (or A&C) vaccine where MenC immunisation has only recently been given.

4.5 The Department has worked with the Muslim Council of Britain to make this information widely available to the Muslim community. An A4 poster with information for the public has been distributed to Mosques and copies are available from the Immunisation Team at the Department of Health. Versions of the poster in Arabic, Bengali and Urdu are available on www.doh.gov.uk/traveladvice/hajj.htm

5. INFLUENZA IMMUNISATION

5.1 Congratulations are due to all those involved in the influenza immunisation programme for 2000/01. Preliminary data show a national uptake of vaccine in those aged 65 and over of 65%, with 91% of Health Authorities reaching the target of at least 60% which was set for the first time.

5.2 It is now time to start planning for next winter. The World Health Organisation has announced their recommendations for the virus strains to be included in the 2001/02 vaccine, and manufacturers are already making their production plans. These include having to place their orders for the eggs on which the vaccine viruses will be grown, which is the main volume-limiting factor in the production of influenza vaccines.

5.3 Full details of the immunisation programme for next year will be issued shortly. In the meantime, practices must assess their vaccine needs for their risk groups. **This requires lists or registers to be made to include all patients aged 65 and over, those in residential care, and those under 65 in the 'high risk' groups:**

RISK GROUPS FOR INFLUENZA IMMUNISATION

<i>Those with chronic respiratory disease, including asthma</i>	This includes chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis, asthma requiring continuous or repeated use of inhaled or systemic steroids or with previous exacerbations requiring hospital admission.
<i>Those with chronic heart disease</i>	This includes chronic ischaemic heart disease, congenital heart disease and hypertensive heart disease requiring regular medication and follow-up (but excluding uncomplicated controlled hypertension), and chronic heart failure.
<i>Chronic renal disease</i>	Including nephrotic syndrome, chronic renal failure, renal transplantation.
<i>Diabetes</i>	Diabetes mellitus requiring insulin or oral hypoglycaemic drugs.
<i>Immunosuppression</i>	Due to disease or treatment, including systemic steroids equivalent to 20mg prednisolone daily for more than 2 weeks. <i>However, please note that some immunocompromised patients may have a suboptimal immunological response to vaccine.</i>

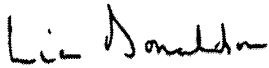
Hospitalisation for any of the above conditions within the last year would be an indication for flu vaccine.

5.4 Some categories of medication nearly conform to the risk criteria. However, they are not concordant with the risk groups and it is recommended they are only used as an ancillary aid in compiling disease-based registers.


5.5 Orders for vaccine for the 2001/02 season should be placed as soon as possible.

6. ANAPHYLAXIS MANAGEMENT.

Agreement has been reached between JCVI, the Resuscitation Council and the BNF, on the dosage guidelines for adrenaline to be given, and the route of administration, in cases of anaphylaxis following immunisation⁽⁹⁾. This clarified guidance is given at Annex 3 to this letter.



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- (1) Adverse Drug Reactions and Toxicological Reviews 2000, 19(4), 265-283.
- (2) Department of Health Press Release 2001/0027, 12 January 2001 (<http://tap.ccta.gov.uk/doh/intpress.nsf/page/2001-0027>); Public Health Link CEM/CMO/2001/1 (12 January 2001).
- (3) BMA Press Release 'Joint professional statement on MMR' 12 January 2001 (<http://web.bma.org.uk/pressrel.nsf>).
- (4) PL/CMO/99/2, PL/CNO/99/4, PL/CPHO/99/1; PL/CMO/99/4, PL/CNO/99/8, PL/CPHO/99/3; PL/CMO/99/5, PL/CNO/99/9, PL/CPHO/99/4 (www.doh.gov.uk/cmo/cmo2.htm).
- (5) Department of Health Press Release 2001/0007, 3 January 2001 (<http://tap.ccta.gov.uk/doh/intpress.nsf/page/2001-0007>).
- (6) UK Health Departments: 'Immunisation against Infectious Disease'. London: HMSO, 1996.
- (7) Working Party of the British Committee for Standards in Haematology Clinical Haematology Task Force. Guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. BMJ 1996; 312: 430-4.
- (8) CDSC. Meningococcal infection in pilgrims returning from the Hajj. CDR Weekly 200; 10: 125, 149 and 169.
- (9) Royal Pharmaceutical Society of Great Britain and British Medical Association. British National Formulary BNF No.40, p155, September 2000, Pharmaceutical Press, London.

ANNEX 1

MMR QUESTIONS AND ANSWERS**1. General statement on safety of MMR vaccine**

The suggestion of an association between measles, measles vaccine, MMR vaccine, inflammatory bowel disease (IBD/Crohn's disease) and autism was made by researchers at the Royal Free Hospital, London, led by Dr Andrew Wakefield. Rigorous scrutiny by the Department of Health and a number of independent expert advisory groups has established that the present evidence does not support any such association.

2. What has the Government done on this concern?

The Government has ensured this issue has been thoroughly looked at. The view of our independent expert committees – the Joint Committee on Vaccination and Immunisation (JCVI) and the Committee on Safety of Medicine (CSM) - remains that, on the scientific evidence available, there is no causal link between MMR vaccine and long term health problems such as bowel disease or autism. This view is supported by non government organisations such as the Medical Research Council (MRC) and World Health Organisation which recognises MMR as being a “highly effective vaccine which has such an outstanding safety record”.

3. Does MMR cause autism and Inflammatory Bowel Disease?

Reviews by both the CSM and the MRC did not identify a causal link between MMR and Measles/Rubella vaccines, autism and IBD. Such views are further reinforced by the report of a CSM Working Party and by a study undertaken in North Thames region, both of which found no evidence of a causal link between MMR and autism, by the latest report from the MRC's group of experts and also by recently published research from the UK.

4. What about the article published in the journal Adverse Drug Reactions and Toxicological Reviews on 21 January 2001 by Wakefield and Montgomery?

The Governments' independent expert committees have reviewed the paper and have advised that: it contains no new data relevant to the safety of MMR vaccine; its analyses are incorrect; and it has failed to mention published work that does not support the hypothesis that MMR causes inflammatory bowel disease and autism.

5. Was MMR vaccine properly tested prior to licensing?

Five combined measles, mumps and rubella vaccines have been licensed in the UK. Three of these are still licensed and two are used in the national immunisation programme (Priorix and MMRII). In accordance with the principles of good clinical practice, the majority of clinical trials that supported licensure of these vaccines were sponsored by the company, were conducted by investigators experienced in the field, and were monitored by company personnel.

After careful review, the Department of Health and the Medicines Control Agency (MCA) reject any suggestion that combined measles, mumps and rubella (MMR) vaccines were licensed prematurely. The Department of Health and the MCA are confident that the licensing process was properly conducted on the basis of safety, quality and efficacy of the vaccines in adequate numbers of children.

Most of the studies enrolled children in the second year of life, although some enrolled children up to 13 years old. Details of adverse reactions were mostly recorded over 4-6 weeks post-injection because children returned for assessment of their response to the vaccines around this time. In clinical trials fewer than 200 children were followed for one year. However, post-marketing reporting of adverse reactions provides much additional information on the safety of these products.

- In 1972 the first measles, mumps and rubella combination vaccine was licensed in the UK (**MMR-I**). Information on protection in nearly 900 previously non-immune children and safety information on about 2,000 children was available.
- **MMR-II** replaced MMR-I in 1987. Detailed safety data were available for more than 800 children who received MMR-II in clinical trials.
- The approval of **Pluserix** in 1988 (not now licensed) was based on data from more than 600 children.
- The approval of **Priorix** in 1997 was based on trials in which almost 6000 children received the vaccine.
- The approval of **Immavax** in 1989 (licensed but not in use in the UK) was based on clinical studies in which at least 6,400 subjects received the vaccine.

By the time the UK came to introduce MMR in 1988, there had already been substantial use in Scandinavia and the USA. Currently MMR is used in over 90 countries worldwide. Over 500 million doses have been given.

6. Has the safety of MMR been looked at in other countries?

Research conducted in Scandinavian countries has looked at measles infection and MMR vaccination in relation to reports of autism and Crohn's disease. In common with the latest information from the UK, no causal link was found between measles infection and MMR vaccination and either autism or Crohn's. For example, a study conducted in Gothenburg, Sweden over a ten year period during which time MMR vaccine was introduced into the childhood immunisation programme, showed that the incidence of autism was unaffected by the introduction of MMR.

7. Do some children develop autism after vaccination?

MMR vaccine is first given between the ages of 13 and 15 months. Autism is frequently diagnosed in the second year of life. This means that purely by chance, some children would have developed their autism around the time of vaccination. Expert reviews have not shown a cause and effect between MMR and autism.

8. Should MMR vaccine be given as 3 separate vaccines?

The UK has never recommended three separate injections. We are not aware of any country that recommends single vaccines rather than MMR. The policy is not based on financial considerations but on the best way to protect children. If there were any evidence of real risk the Department of Health would act immediately. By contrast, separating vaccines puts children at risk and there is no evidence of a benefit over MMR. It is vital for children to be immunised with MMR or these three diseases will return.

9. What are the risks in using single vaccines?

- There is no convincing evidence of any additional benefit from using single vaccines instead of MMR.
- There is very considerable evidence for the safety of MMR vaccine. The WHO stated on 24 January 2001: "WHO strongly supports the use of MMR vaccine on the grounds of its convincing record of safety and efficacy. The combination vaccine is recommended rather than monovalent presentation [single vaccines] when available and the disease burden justifies its use".
- Separating the vaccines – it has been suggested, without any scientific evidence, that there should be a gap of at least 12 months between vaccines – leaves children at risk of infection whilst waiting between vaccines.
- Children would be left at risk up to age 3 years from either measles (which is potentially a very serious disease) or rubella (with the risk to the unborn child this brings for unprotected pregnant women) or mumps (which, before MMR, was introduced was the main cause of viral meningitis).

- As six injections would be required rather than two, separating the vaccines exposes children to the risks of repeated reactions at the site of injection.

10. Can you get single measles and mumps vaccines privately?

The importation of unlicensed vaccine when a licensed alternative is available is restricted under the Medicines Act and this restriction applies equally to NHS and private sectors.

11. Why are single measles and mumps vaccines not available?

Although licenses for single measles and mumps vaccines do exist in the UK, no licensed single measles or mumps vaccines are manufactured for, or available for, the UK market. The MCA has restricted the importation of single measles and mumps vaccines on the grounds that under law, unlicensed medicines should not be imported when a safe and effective licensed alternative which meets a patient's needs – that is, MMR – is available. The MCA was also concerned about the evidence that the single mumps vaccine (Rubini strain) being imported was ineffective and that the mumps Urabe strain was less safe. Neither of these two vaccines can now be imported.

12. Other countries

No country in the world recommends MMR be given as 3 separate vaccines. MMR is used in 93 countries around the world. Over 500 millions doses have been given worldwide. Single rubella vaccine is available in the UK as it is recommended for women who are not immune. France has been mentioned as a country where single vaccines are given. However, the position is that in France children are given single measles vaccine from 9 months of age **IF** they are in a nursery and there is a risk of a measles outbreak. These children then receive 2 further MMR vaccinations, at the same time as the UK. France does not recommend single mumps vaccine.

13. Situation in Japan

Japan immunises against measles and rubella separately because they do not have a suitable MMR vaccine. However, Japan has suffered from endemic and epidemic measles. Between 1992-97, there were 79 measles deaths in Japan. There have been no deaths from acute measles in the UK since 1992. There is no recent data on CRS prevention in Japan. Between 1997 and 1999, there were no cases of CRS in England and Wales detected through active surveillance.

14. MMR vaccine contains 3 viruses in one: is this too much for young children?

Evidence shows that babies' and young children's immune systems cope daily, without difficulty, with many different challenges from the wild viruses and bacteria that are found virtually anywhere. In addition, the three vaccines in MMR work at different speeds, so they don't all impact on the child at once. Splitting MMR into separate doses may be harmful because it exposes children unnecessarily to potentially serious diseases.

15. Consequences of fall in MMR vaccine uptake

MMR vaccine uptake has fallen over the past few years at age two and has now stabilised at around 88%. This is too low to maintain sufficient levels of protection in the population, especially against measles (95% is needed). We are very close to the point where serious outbreaks of measles will occur as in Ireland where there have been deaths from measles. Mumps and rubella may not be far behind. Every child who is not immunised is at risk and also increases the risk of a return of these potentially very serious diseases. The latest scientific evidence shows MMR remains the safest way to protect children against these diseases.

In addition, further information can be found on each of the following web sites:

www.immunisation.org.uk

www.doh.gov.uk

www.open.gov.uk/mca

ANNEX 2

**IMMUNISATION FOR PILGRIMS TRAVELLING TO SAUDI ARABIA
FOR HAJJ OR UMRAH**

1. Last year, an outbreak of meningococcal W135 infection was associated with the Hajj⁽⁸⁾ The UK therefore now recommends that the quadrivalent meningococcal polysaccharide vaccine, which provides protection against A, C, W135 and Y strains, is more appropriate.
2. One licensed product, 'ACWY Vax' (SmithKline Beecham), is available and the details are as shown below.
3. 'ACWY Vax' comes in a vial containing one dose of 0.5ml freeze-dried vaccine with an ampoule of diluent for reconstitution. It is recommended for both adults and children aged two years and over. Children 2 months to 2 years who are at particular risk of infection may also be immunised. However, although immune responses may be achieved to serogroup A, W135 and Y antigens in children less than 2 years old, the degree of protection may be unreliable and is likely to be short-lived. The vaccine should not be used in infants of less than two months.
4. 'ACWY Vax'▼ will be supplied in the following pack sizes:-

SB Code	Product	Pack size	Trade Price (excl VAT)	Order in multiples of	IMS Code	PIP Code	EAN Number
7309	ACWY Vax	1	£17.14	1	SCVM	275-8167	5000483730901

Ordering - With immediate effect, all orders for 'ACWY Vax' should be directed to your usual wholesaler/supplier:

5. For further information please contact:

Customer Response Centre
SmithKline Beecham Pharmaceuticals
Mundells
Welwyn Garden City
AL7 1EY

Freephone orders: 0808 100 9997
Freephone Enquiries: 0808 100 2228

ANNEX 3

ANAPHYLAXIS GUIDANCE

The dosage guidelines for adrenaline to be given, and the route of administration, in cases of anaphylactic reactions in children following immunisation by First Medical Responders is as follows:

	Adrenaline (epinephrine) <u>1:1000</u> solution ⁽ⁱ⁾
>12 years:	500 micrograms IM (0.5 ml) 250 micrograms if child is small or prepubertal ⁽ⁱⁱ⁾
6-12 years:	250 micrograms IM (0.25ml) ⁽ⁱⁱ⁾
> 6 months–6 years:	120 micrograms IM (0.12ml) ⁽ⁱⁱ⁾
< 6 months:	50 micrograms IM (0.05ml) ⁽ⁱⁱⁱ⁾

- (i) For profound shock, judged **immediately** life threatening, give CPR/ALS if necessary. Consider **slow** intravenous (IV) adrenaline (epinephrine) 1:10,000 solution. This is **hazardous** and is recommended only for an experienced practitioner who can also obtain IV access without delay. Note the different strength of adrenaline (epinephrine) that may be required for IV use.
- (ii) For children who have been prescribed EpiPen, 150 micrograms can be given instead of 120 micrograms, and 300 micrograms can be given instead of 250 micrograms.
- (iii) A crystalloid may be safer than a colloid.

