

From the Chief Medical Officer  
Dr Henrietta Campbell CB



Department of  
**Health, Social Services  
and Public Safety**

An Roinn

**Sláinte, Seirbhísí Sóisialta  
agus Sábháilteachta Poiblí**

[www.dhsspsni.gov.uk](http://www.dhsspsni.gov.uk)

Castle Buildings  
Stormont Estate  
BELFAST BT4 3SQ  
Tel: 028 90520563  
Fax: 028 90520574  
Email: [henrietta.campbell@dhsspsni.gov.uk](mailto:henrietta.campbell@dhsspsni.gov.uk)

Your Ref:

Our Ref: HSS(MD)12/2004

Date: 8<sup>th</sup> April 2004

## URGENT COMMUNICATION

**HSS(MD)12.2004**

To:

- All General Practitioners
- Directors of Public Health, HSS Boards (*for onward distribution to Duty Doctors in Public Health Medicine*)
- Consultants in Communicable Disease Control
- Directors of Pharmacy, HSS Boards and HSS Trusts
- Directors of Nursing, HSS Boards and HSS Trusts
- Medical Directors, HSS Trusts
- All Community Pharmacists
- Dr Sara Hedderwick, Infectious Disease Physician
- Dr Paul Jackson, Infectious Disease Physician
- Dr Paul Rooney, Director of Public Health Laboratory
- Regional Virologists
- Dr Delia Skan, EMAS

Dear Colleague

## RECALL OF RABIES VACCINE BY AVENTIS PASTEUR MSD LTD

The purpose of this urgent communication is to update the earlier communication (Ref: HSS(MD)11-2004) which you received on Tuesday 6<sup>th</sup> April 2004.

The four Health Departments in conjunction with the Health Protection Agency England and the Medicines and Healthcare Products Regulatory Agency (MHRA) have agreed guidance on the management of people who received Rabies vaccine (Aventis Pasteur MSD Batch X0071-6). A copy of the detailed guidance is attached. This guidance is also available on the Health Protection Agency's website at [www.hpa.org.uk](http://www.hpa.org.uk)

The key points to note from this guidance are as follows:

1. The initial vaccine lot containing non-inactivated rabies virus was not distributed.
2. Aventis Pasteur has initiated a voluntary recall of vaccine batches that were manufactured during the same period as the lot that contained non-inactivated virus. Of these only Batch No X0071-6 was distributed in the UK. It is important to note that this batch has passed all of the quality assurance tests required in Europe and the USA and that includes a test to confirm that the virus has been inactivated.
3. Although it is highly unlikely that persons who received a doses of Rabies vaccine from Batch No X0071-6 were exposed to the non-inactivated vaccine strain of Rabies virus a theoretical possibility exists.

## Use of Human Rabies Immune Globulin (HRIG)

Following a detailed risk assessment the UK Health Departments, the Health Protection Agency and the MHRA have taken the decision not to use HRIG in the treatment of affected patients in the UK and Ireland. Detailed information on the risk assessment to inform this decision is included on Page 3 and 4 of the Health Protection Agency's Guidance.

### Action Required

1. Following HSS(MD)11-2004 all remaining doses of vaccine Batch No X0071-6 should now have been quarantined. Any health care providers who are holding stocks of this vaccine and who have not already quarantined it should do so as a matter of urgency.
2. Any person who has received Rabies vaccine since 26<sup>th</sup> February 2004 will need to have checked which vaccine and which batch they have received. A detailed flowchart has been developed in relation to the management of people who have received Rabies vaccine from Batch No X0071-6 and this is attached to the Health Protection Agency's Guidance.
3. Clinicians who require Rabies vaccine over the Easter holiday weekend for the management of any of these patients may obtain vaccine from the Public Health Laboratory at Belfast City Hospital by calling Belfast City Hospital Switchboard on 028 90 329241 and asking for the Consultant Microbiologist On-Call. Alternatively vaccine may be obtained from Community Pharmacists under usual arrangements.
4. Further updates on this situation may be developed over the weekend and will be posted on the website of the Health Protection Agency at [www.hpa.org.uk](http://www.hpa.org.uk)

A detailed Question & Answer Brief is also included with this communication. This is also available on the Department's website at [www.dhsspsni.gov.uk/publichealth](http://www.dhsspsni.gov.uk/publichealth)

Yours sincerely

**Dr Lorraine Doherty**  
**Senior Medical Officer (Communicable Diseases)**

cc: Dr Henrietta Campbell, Chief Medical Officer  
Dr N Morrow, Chief Pharmaceutical Officer  
Miss J Hill, Chief Nursing Officer  
Dr E Mitchell, DHSSPS  
Mr C Shannon, DHSSPS  
Mr G Dorrian, DHSSPS  
Dr Brian Smyth, Regional Epidemiologist

This letter is available at [www.dhsspsni.gov.uk](http://www.dhsspsni.gov.uk) and also on the DHSSPS Extranet which can be accessed directly at <http://extranet.dhsspsni.gov.uk> or by going through the HPSS Web at <http://www.n-i.nhs.uk> and clicking on DHSSPS.

**Recall of Rabies Vaccine Aventis Pasteur MSD: Batch X0071-6  
Advice to Clinicians**

**The Alert**

The Medicines and Health Care Products Regulatory Agency (MHRA) sent an alert to contacts including Chief Pharmacists in England, Scotland, Wales and Northern Ireland, Prison Health Policy Unit, Medical Supplies Agency, Primary Care Trusts, and the National Care Standards Commission on 5<sup>th</sup> April 2004 informing them of a recall of Rabies Vaccine BP (Aventis Pasteur). A recent quality-assurance test identified the presence of non-inactivated Pitman-Moore virus (an attenuated vaccine strain) in a single produce lot that was not distributed.

**The Significance**

The manufacturing process does not use a wild (ie naturally occurring) rabies virus, but rather an attenuated ie weakened strain of virus called the Pitman-Moore vaccine strain. The attenuated vaccine strain has been tested in animal models and has been shown to be less pathogenic than wild rabies virus. The Pitman-Moore strain produces a protective immune response, which is why it is used to make the vaccine. Rabies vaccine BP is developed and marketed as an inactivated vaccine, meaning that any virus in the vaccine has to be killed before it is given to humans. Finding non-inactivated (ie live) virus in a lot after it was manufactured indicates a failure in the manufacturing process, and the vaccine might not be safe to give to humans. The vaccine lot containing non-inactivated virus was not distributed.

**The Recall**

Four other vaccine lots produced around the same time as the vaccine lot containing non-inactivated vaccine passed all of the regulatory testing (including tests for inactivation of virus) and were distributed within the USA and Europe between September 2003 and April 2004. No unusual adverse events have been associated with the receipt of these vaccines.

In advance of retesting of vaccine from these lots, as an additional precautionary measure Aventis Pasteur MSD has initiated a voluntary recall of vaccine batches that were manufactured during the same period as the lot that contained non-inactivated Pitman-Moore virus. Of these, only batch number X0071-6 was distributed in the UK. Other batches were distributed to other countries where similar action is being taken. It is important to emphasise that batch number X0071-6 has passed all of the quality assurance tests required in Europe and the USA and that includes a test to confirm that the virus has been inactivated. Aventis Pasteur MSD is contacting all customers who have been supplied with the specified batch,

**The People Affected**

Batch number X0071-6 was first distributed in the UK on 26<sup>th</sup> February 2004, so this alert only affects people who have received rabies vaccine from that particular batch since that date. Approximately 6,000 doses of this batch of vaccine have been distributed to General Practitioners, Hospitals, Health Centres and Travel Clinics in the UK. Unused vaccine from

batch number X0071-6 has since been quarantined. Anyone who received Rabipur® (the Rabies Vaccine manufactured by Chiron) is not affected.

### **The Action Required**

Any person who has received rabies vaccine since 26<sup>th</sup> February 2004 will need to have checked which vaccine and which batch they received. Although it is highly unlikely that persons who received a dose of rabies vaccine from batch X0071-6 were exposed to the non-inactivated Pitman-Moore vaccine strain of rabies virus a theoretical possibility exists. The timely administration of treatment, as described in the flow chart below, will help to ensure a negligible risk to persons who have received rabies vaccine from batch number X0071-6. Unused vials of batch X0071-6 should be removed from your vaccine stacks and set aside for return to the manufacturers.

### **Human Rabies Immune Globulin (HRIG)**

The issue of whether human rabies immune globulin (HRIG) should be given to patients who have received the recalled batch in the past 7 days has been considered following the vaccine alert by MHRA and the decision has been made not to use it in the treatment of affected patients in the UK and Ireland. This decision is based on a risk assessment which included the following considerations:

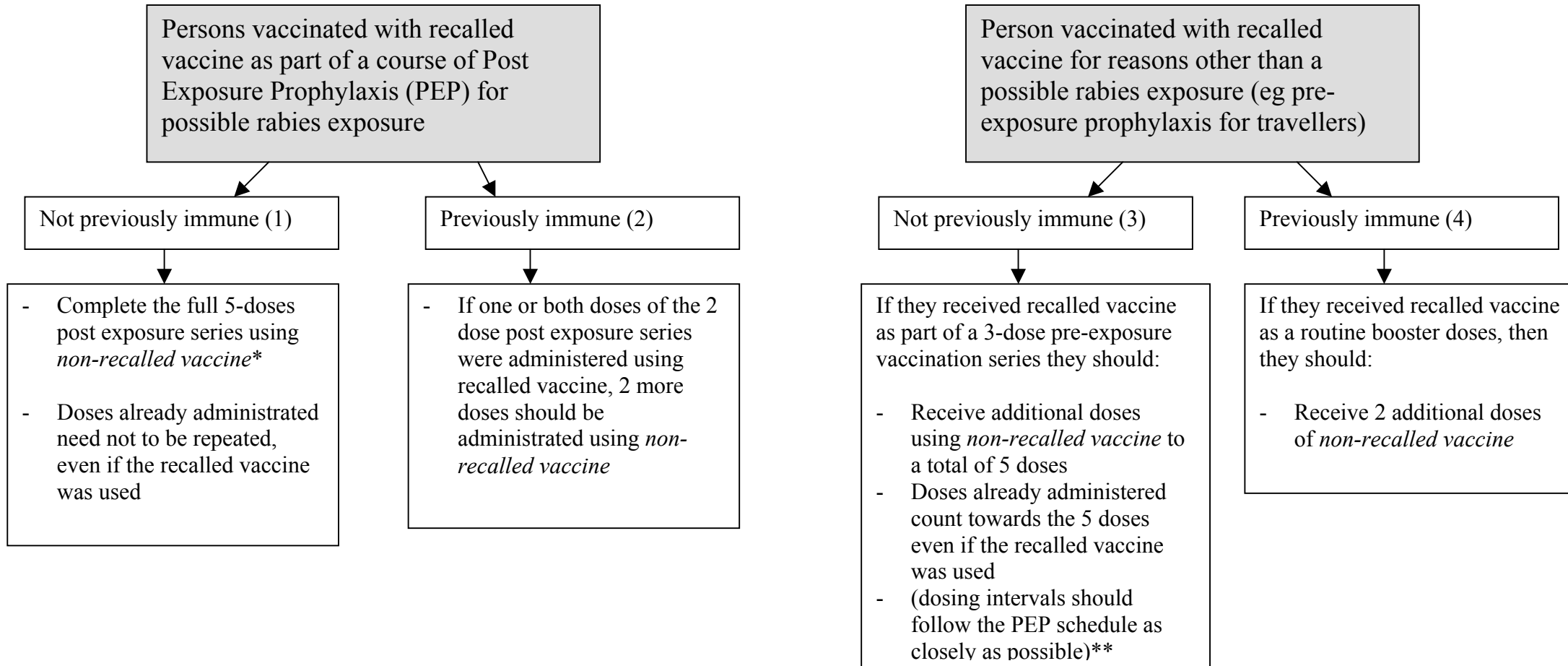
- The risk to patients from this vaccine is defined as very low – described as “negligible if any” or “theoretical”. Current UK procedure for low risk exposures is not to issue HRIG for post-exposure treatment for low risk exposures (Department of Health Immunisation Against Infectious Diseases <http://www.dh.gov.uk/assetRoot/04/07/31/31/04073131.pdf>) but to issue vaccine only. This could also be defined as a Category II exposure according to WHO guidance, which would also not warrant HRIG (<http://www.who.int/docstore/wer/pdf/2002/wer7714.pdf>).
- The US Centers for Disease Control and Prevention (CDC) and FDA approved protocol for managing exposures to this vaccine (<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm53d402a1.htm>) advises use of HRIG but CDC have supported taking a different approach in different countries ([http://www.cdc.gov/ncidod/dvrd/rabies/ques&ans/q&a\\_vaccine\\_recall.htm](http://www.cdc.gov/ncidod/dvrd/rabies/ques&ans/q&a_vaccine_recall.htm))
- The negligible risk of problems in individuals receiving vaccines from these batches is underscored by the fact that the vaccine virus is highly attenuated and that all recalled vaccine batches have passed both EU and FDA tests for inactivation of virus. Note the vaccine batch that failed the US regulatory test was not distributed.
- No unusual adverse events are known to have occurred following administration of the recalled lots of IMOVAX (the name of Rabies Vaccine BP in the USA) vaccine. Recalled lots have been in use in the USA since September 23<sup>rd</sup> 2003 without any unusual adverse events being reported. This includes both surveillance of neurological events reported through the Vaccine Adverse Event Reporting Scheme (VAERS) and reports of clinical rabies. No human cases of rabies have ever been transmitted through currently licensed rabies vaccine products in the UK.
- The potential demand for HRIG to supply this recall event will use up currently available HRIG stocks in the United Kingdom. This is in short supply in most countries. As it cannot easily be sourced from elsewhere, current UK stocks must be safeguarded to protect patients from genuine high risk exposures (for example someone bitten by an animal suspected to have rabies while abroad who is now seeking treatment on return to the UK).

- HRIG is a pooled human plasma product, prepared using a variety of inactivating steps and viewed as a safe product. However the low to negligible risks to patients who have received the recalled vaccine batch should be balanced against theoretical risks of human blood products.

## **Vaccine**

The required doses of vaccine for post-exposure treatment of patients are show in the accompanying flowchart. Aventis Pasteur MSD is working to source additional supplies of Rabies Vaccine BP and will contact customers as soon as these doses become available. Aventis Pasteur MSD will also re-imburse the costs of vaccinating patients affected by this recall if immediatly available vaccine has already been used for this purpose. Aventis Pasteur MSD will be contacting customers with further information about this. An alternative vaccine, Rabipur is available from MASTA on 0113 238 7500. Rabies Vaccine BP and Rabipur may be used interchangeably in post-exposure vaccination.

## Recommendation for people who received rabies vaccine (Aventis Pasteur MSD: Batch X0071-6)



1. Persons who have not received at least 3 doses of vaccine at some point before the possible rabies exposure.
2. Persons who have received at least 3-doses of vaccine at some point before the possible rabies exposure (eg a full, pre or post-exposure vaccination series).
3. Persons who have not received at least 3 doses of vaccine at some previous time.
4. Persons who have received at least 3-doses of vaccine at some previous time (eg a full, pre or post-exposure vaccination series)

\* *Non-recalled vaccine*: Either non-recalled vaccine from the same manufacturer (Aventis Pasteur MSD Ltd) or any other human diploid cell derived vaccine (for example Chiron). MASTA who distribute RABIPUR manufactured by Chiron. MASTA can be contacted on 01132387500

\*\* Post-Exposure Vaccine Schedule is day 0,3,7,14 and 30

## **Recall of Rabies Vaccine BP Batch X0071-6 (Aventis Pasteur MSD)**

### **Q&A**

#### **Q: What lots have been recalled and why?**

A: In the United Kingdom, the recall affects Rabies Vaccine BP Batch Number X0071-6 which was produced during the same time period as the non-distributed batch containing non-inactivated Pitman-Moore virus. The lots recalled internationally including X0071-6 passed all release tests, including testing to confirm the absence of live virus. They are being recalled only as a precautionary measure.

#### **Q: When were these lots distributed in the United Kingdom?**

Only batch number X0071-6 was distributed in the UK, first on 26th February 2004. So this alert only affects people who have received rabies vaccine from that particular batch since that date. Approximately 6,000 doses of this batch of vaccine have been distributed to General Practitioners, Hospitals, Health Centres and Travel Clinics in the UK.

#### **Q: What is the significance of finding non-inactivated virus in the vaccine?**

A: Rabies Vaccine BP is developed and marketed as an inactivated vaccine, meaning that any virus in the vaccine has been killed before it is given to humans. Finding non-inactivated (i.e., live) virus in a batch after it was manufactured indicates a failure in the manufacturing process, and the vaccine may not be safe to give to humans. It is important to note that no batches containing non-inactivated virus are known to have been distributed; the recall is a precautionary measure.

#### **Q: What does “attenuated strain of rabies virus” mean?**

A: The manufacturing process does not use a wild (i.e., naturally occurring) rabies virus, but rather an attenuated or weakened (also known as “fixed”) strain of virus called the Pitman-Moore vaccine strain. The attenuated vaccine strain has been tested in animal models and has been shown to be less pathogenic than wild rabies virus. However, the Pitman-Moore strain produces a protective immune response, which is why it is used to make the vaccine.

#### **Q: Does the recall affect vaccine that was distributed in other countries?**

A: The manufacturer has indicated that additional batches of recalled vaccine were distributed internationally. More than 20 countries are affected by the recall. Similar to the batch recalled in the UK, the internationally distributed batches passed all release tests, including testing to confirm the absence of live virus.

The manufacturer is working with regulatory authorities to determine batch numbers of vaccine and countries that may have received recalled vaccine.

**Q: What should providers and distributors do with any remaining vaccine doses from recalled lots?**

A: General Practitioners, Hospitals, Health Centres and Travel Clinics in the UK who have any remaining doses of lot X0071-6 should not use them but should quarantine the remaining doses. Aventis Pasteur MSD is contacting all distributors and providers with additional detailed information on their disposal.

**Q: I am a healthcare provider treating a patient who received recalled vaccine-what should I do?**

A: Healthcare providers who are treating a patient who received a dose of rabies vaccine since February 26<sup>th</sup> 2004 should check the patient's record to verify whether they received a dose from batch number X0071-6. They should treat persons who have received recalled vaccine according to the recommendations outlined in:

[http://www.hpa.org.uk/infections/topics\\_az/rabies/Rabies\\_Vaccine\\_Recall.pdf](http://www.hpa.org.uk/infections/topics_az/rabies/Rabies_Vaccine_Recall.pdf)

**Q: I received a dose of the recalled vaccine - could I develop rabies?**

No unusual adverse events—and in particular, no cases of vaccination-induced rabies—are known to have occurred following administration of the recalled batches of rabies vaccine. Recalled batches have been in use in the USA since September 23<sup>rd</sup> 2003 and in Ireland since October 24<sup>th</sup> 2003 without any unusual adverse events being reported. Nevertheless, although this is a highly attenuated strain of vaccine virus, it could theoretically cause rabies in humans. No human case of rabies has ever been transmitted through currently licensed rabies vaccine products in the UK.

It is extremely important that all patients currently receiving a rabies vaccination series (e.g. for travel overseas) complete their immunisation series on time, using non-recalled vaccine. Do not omit any injections that have not yet been administered, and do not delay their administration.

**Q: I received a dose of rabies vaccine since February 26<sup>th</sup> 2004 but I am not sure if I received recalled vaccine - what should I do?**

A: Anybody who has received rabies vaccine since February 26<sup>th</sup> should be contacted by the surgery/travel clinic that administered the rabies vaccine if they received a dose of the recalled batch of vaccine. If in doubt, patients should check with the surgery/travel clinic that administered the vaccine(s).

Anyone who received RABIPUR (the rabies vaccine manufactured by Chiron) is not affected. Anyone who received an Aventis Pasteur MSD rabies vaccine from a batch different to X0071-6 since February 26<sup>th</sup> is not affected.

**Q: Who will pay for the costs of revaccination?**

A: Aventis Pasteur MSD is working to source additional supplies of Rabies Vaccine BP and will contact customers as soon as these doses become available. Aventis Pasteur MSD will also re-imburse the costs of vaccinating patients affected by this recall if immediately available vaccine has already been used for this purpose. Aventis Pasteur MSD will be contacting customers with further information about this.

**Q: Is the identification and treatment of persons who received recalled vaccine considered a medical emergency?**

A: It is important to keep in mind that none of the recalled batches were known to contain non-inactivated virus and that the recall is being initiated as a precaution. While the situation is urgent and warrants a diligent approach by healthcare providers, it is not a medical emergency. Every effort should be made to contact the patient to inform them of the alert.

**Q: How should persons who completed a 3-dose pre-exposure vaccination series in which recalled vaccine was given be treated?**

A: Persons who have completed a full 3-dose pre-exposure series in which recalled vaccine was used should receive 2 additional doses of vaccine, regardless of how much time has elapsed since the last dose of vaccine. Dosing intervals should follow the post-exposure prophylaxis (PEP) schedule as closely as possible (i.e. Day 0,3,7,14, 30).

**Q: Do persons who completed a 3-dose pre-exposure vaccination using recalled vaccine and who are now overseas need to return to the UK**

A: If they have received rabies vaccine from batch number X0071-6 as part of a 3 dose pre-exposure prophylaxis then they require two additional doses using non-recalled vaccine while abroad or, failing this, on their return to the UK.

Aventis Pasteur MSD are advising travelers to contact the relevant British Embassy for referral to a reliable medical centre while abroad. Travelers should keep all receipts for reimbursement by Aventis Pasteur MSD. If travelers who were vaccinated with the recalled batch return without having been vaccinated while abroad, they should seek attention immediately to ensure that they complete the required number of doses as soon as possible.

**Q: How should persons who have started but not yet completed a 3-dose pre-exposure vaccination series in which recalled vaccine was given be treated?**

A: For persons who have not yet completed all 3 doses of the series (i.e., only received 1 or 2 doses), give additional doses to complete a total of 5 doses including the doses of recalled vaccine already given. Dosing intervals should follow the PEP schedule as closely as possible (i.e. Day 0,3,7,14, 30)

**Q: How should persons who have completed a full 5 dose pre-exposure vaccination series in which recalled vaccine was given be treated?**

A: Persons who have completed a full 5-dose post-exposure series in which recalled vaccine was used do not require any further doses of vaccine.

**Q: How should persons who have started but not yet completed a 5-dose post-exposure vaccination series in which recalled vaccine was given be treated?**

A: Persons should complete the full 5 doses post exposure series using non-recalled vaccine. Doses already administered need not be repeated, even if the recalled vaccine was used. Dosing intervals should follow the post-exposure prophylaxis (PEP) schedule as closely as possible (i.e. Day 0,3,7,14, 30)

**Q: How should persons who have received recalled vaccine as a single booster dose be treated?**

A: Persons who have received recalled vaccine as a booster dose should receive 2 additional doses of non-recalled vaccine, one immediately and one 3 days later.

**Q: Are the medical recommendations for persons who have received recalled vaccine different for pregnant or breastfeeding women**

A: Rabies vaccine is not contraindicated during pregnancy or while breastfeeding, and the recommendations for treatment of persons who received recalled vaccine do not differ for pregnant or lactating women. Even if a pregnant or lactating woman is exposed to rabies, her unborn or breastfeeding infant is not at risk unless the mother develops clinical signs of infection. Following the recommendations outlined by HPA will help to ensure negligible risk. These can be found at:

[http://www.hpa.org.uk/infections/topics\\_az/rabies/Rabies\\_Vaccine\\_Recall.pdf](http://www.hpa.org.uk/infections/topics_az/rabies/Rabies_Vaccine_Recall.pdf)

**Q: How should persons who do not fit the current medical recommendations be treated?**

A: The situations for which rabies vaccine may be administered vary widely, and it is possible that some persons may have received recalled vaccine under circumstances not addressed here. Persons seeking clarification for unusual circumstances may contact the duty doctor at the Health Protection Agency, Specialist and Reference Microbiology Division (Tel: 020 8200 4400) or HPA Communicable Disease Surveillance Centre (Tel. 0208 200 6868)