Public Health England

Protecting and improving the nation's health

# Recommendations on the treatment and prophylaxis of tetanus

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# Background

National guidelines on the management of tetanus prone injuries and clinically suspected tetanus cases are published and updated by Public Health England (PHE).

For tetanus-prone injuries, based on a risk assessment on the nature of the wound and immunisation status of the individual, a reinforcing dose of tetanus containing vaccine and/or of a prophylactic dose of tetanus immunoglobulin (TIG), given intra-muscularly. The recommended treatment for clinically suspected cases of tetanus is an IV preparation.

The supply of tetanus immunoglobulin (TIG) has been limited for a number of years and an IV-TIg product is no longer available in the UK. The use of normal preparations of immunoglobulin (for intravenous (IV) and sub-cutaneous / intramuscular use) has been recommended as an alternative since it contains reasonable levels of tetanus antibody when measured by ELISA. Recommendations for use of specific products was based on testing of commonly used products, Subgam (for tetanus-prone injuries) and Vigam (for suspected clinical cases) by the National Institute of Biological Standards (NIBS) for anti-tetanus antibodies. Testing revealed a good correlation between ELISA and in vivo Toxin Neutralising Test (TNT) anti-toxin assays for both Vigam and Subgam. The levels detected were used to estimate the equivalent doses of normal immunoglobulin to achieve the recommended dose of tetanus anti-toxin.

In April 2018, updated interim guidance for the treatment of clinically suspected tetanus cases, was issued in response to changes in available IV immunoglobulin products in the NHS. Based on testing carried out by NIBSC of seven other IV immunoglobulin products to determine if they have similar levels of tetanus antibody, it was recommended that they may used as alternatives to previously tested products.

PHE has recently become aware of a severe shortage of IM-TIG and Subgam available in the NHS for the management of tetanus prone wounds. Furthermore the alternative HNIG products that are approved for use by NHS England are also in limited supply. As a consequence, PHE have urgently reviewed the existing evidence and data to prioritise the use of TIG /HNIG for susceptible individuals who have sustained high risk injuries, and are at greatest risk.

Guidance for classifying tetanus-prone injuries has also been revised.
**This advice supersedes recommendations in the current tetanus advice for health professionals:**
https://www.gov.uk/government/publications/tetanus-advice-for-health-professionals
and the Green Book.
https://www.gov.uk/government/publications/tetanus-the-green-book-chapter-30

Full details will be issued in the revised PHE Guidelines for Management of Clinical Tetanus and of Tetanus-prone Wounds, which will be published in 2018. However, in light of current stock shortages, these interim recommendations regarding immunoglobulin use for treatment and prophylaxis are published here in advance of the main guidance document.

# Recommendations:

## 1. Management of tetanus prone wounds

Tetanus-prone wounds include:

- puncture-type injuries acquired in a contaminated environment and likely therefore to contain tetanus spores e.g. gardening injuries
- wounds containing foreign bodies
- compound fractures
- wounds or burns with systemic sepsis
- certain animal bites and scratches – although smaller bites from domestic pets are generally puncture injuries animal saliva should not contain tetanus spores unless the animal has been routing in soil or lives in an agricultural setting

Note: individual risk assessment is required and this list is not exhaustive e.g. a puncture- wound from discarded needle found in a park may be a tetanus-prone injury but a needlestick injury in a medical environment is not.

High-risk tetanus-prone wounds include:

Any of the above with either:

- heavy contamination with material likely to contain tetanus spores e.g. soil, manure
- wounds or burns that show extensive devitalised tissue
- wounds or burns that require surgical intervention that is delayed for more than six hours are high risk even if the contamination was not initially heavy

Thorough cleaning of wounds is essential. If the wound, burn or injury fulfils the above criteria, IM-TIg or HNIG for subcutaneous use, and/or a reinforcing dose of tetanus-containing vaccine should be given for immediate and long-term protection, according to the recommendations in the Table overleaf.

## Tetanus Immunisation and Prophylaxis Following Injuries

| Immunisation Status | Immediate treatment | | | Later treatment |
|---|---|---|---|---|
| | Clean wound | Tetanus Prone | High risk tetanus prone | |
| Those aged 11 years and over, who have received an adequate priming course of tetanus vaccine[1] with the last dose within 10 years<br><br>Children under 5 years who have received an adequate priming course | None required | None required | None required | Further doses as required to complete the recommended schedule (to ensure future immunity) |
| Received adequate priming course of tetanus vaccine[1] but last dose more than 10 years ago<br><br>Children aged 5-10 years who have received an adequate priming course but no preschool booster<br><br>*Includes UK born after 1961 with history of accepting vaccinations* | None required | Immediate reinforcing dose of vaccine | Immediate reinforcing dose of vaccine<br><br>One dose of human tetanus immunoglobulin[2] in a different site | Further doses as required to complete the recommended schedule (to ensure future immunity) |
| Not received adequate priming course of tetanus g vaccine[1]<br><br>*Includes uncertain immunisation status and/or born before 1961* | Immediate reinforcing dose of vaccine | Immediate reinforcing dose of vaccine<br><br>One dose of human tetanus immunoglobulin[1] in a different site | Immediate reinforcing dose of vaccine<br><br>One dose of human tetanus immunoglobulin[2] in a different site | |

1. At least three doses of tetanus vaccine 2. If TIG is not available, HNIG may be used as an alternate

## Rationale for interim changes in guidance

In the UK, 5 doses of tetanus containing vaccine are routinely offered. The primary series of tetanus containing vaccine is at 2, 3 and 4 months of age, and then a school-entry booster is recommended at 3 years 4 months. Although antibody levels decline around five years after the primary series in infancy, there is an excellent response to the booster at 3 years 4 months of age and antibody levels persist at least until age 14, when the adolescent booster dose also results in rapid and high increase in antibody. A recent WHO review concluded that following the primary series, typically immunity persists for 10 years after the fourth dose and for at least 20 years after the fifth dose (WHO, The Immunological Basis for immunization series Module 3: Tetanus Update 2018, under review). Universal vaccination was introduced into the UK in 1961.

The rationale for using IM-TIG in at-risk individuals is to sufficiently and rapidly raise antibody levels in exposed individuals who cannot rely on immune memory – peak levels are achieved 4 days after an IM dose. In individuals who have completed a full primary course, a measurable increase in antibody titres following a vaccine booster has been observed as early as 4 days, but levels increase substantially from day 7. The median incubation period for tetanus is reported as 7 days but can range from 4-21 days and therefore it is important that either TIG or active boosting occurs promptly following an exposure. It has also been shown that the antibody levels achieved 5-7 days after a reinforcing dose of vaccine likely exceeds the estimated antibody boost from a prophylactic dose of im TIG in an adult.

**Recommended dose of IM-TIG**

The recommended dose of intramuscular TIG is:

- 250 (IU) for most uses
- 500 IU if more than 24 hours have elapsed or there is risk of heavy contamination or following burns

The dose is the same for both adults and children.

IM-Tig is available in 1ml ampoules containing 250 units (IU). If TIG (for intramuscular use) cannot be sourced, Human Normal Immunoglobulin (HNIG) for subcutaneous or intra-muscular use may be given as an alternative. Based on testing for the presence of anti-tetanus antibodies of one HNIG product, Subgam 16%, the volume of Subgam 16% required to achieve the recommended dose of 250IU is approximately 5mls – equivalent to one vial of 750mg. PHE has not undertaken formal testing of other available HNIg products for subcutaneous use but similar levels of anti-tetanus potency are likely, based on their immunoglobulin concentration.

**The dose guidelines for management of tetanus prone wounds using IM-Tig or HNIG for subcutaneous use are summarised in the Table**

| Indications | Im-Tig | Subgam 16% (HNIG for IM or SC use) |
|---|---|---|
| For most uses | 250 IU | 750mg |
| If more than 24 hours have elapsed **and** there is risk of heavy contamination or following burns. | 500 IU | 1500mg |

NHS Trusts should source supplies of immunoglobulin for management of tetanus prone wounds directly from the manufacturer.

## 2. Treatment of Clinical Tetanus with Intravenous Immunoglobulin (IVIG)

Early treatment with human intravenous immunoglobulin (IVIG) can be lifesaving and its use should be considered based on a clinical assessment. An IV tetanus immunoglobulin (TIG) product is no longer available in the UK. In the absence of IV TIG, IVIG is the recommended treatment for clinical suspected tetanus. This is based on previous testing of the IVIG product Vigam 5% for anti-tetanus antibodies, which was carried out by NIBSC and showed that Vigam contained reasonable levels of tetanus antibody when measured by ELISA which correlated well with *in vivo* Toxin Neutralising Test (TNT) anti-toxin assays. More recently, seven other IVIG products that are commonly available to NHS Trusts: Gammaplex 5%, Privigen 10%, Octagam 10%, Intratect (5% & 10%) and Flebogama (5% & 10%) have been tested for the presence of anti-tetanus antibodies and have been shown to be comparable in terms of their anti-tetanus potency (see Appendix).

The recommended dose of anti-tetanus antibodies is based on weight:

- for individuals less than 50 kg, 5,000 IU (international units)
- for individuals over 50 kg, 10,000IU

The volume of human IVIG required to achieve the recommended dose of anti-tetanus antibodies is:

| IVIg Products tested for anti-tetanus antibodies | Volume required (in ml) | |
|---|---|---|
| | For individuals < 50kg | For individuals > 50kg |
| Gammaplex 5%, Intratect 5%, Flebogamma 5%, Vigam 5% | 400ml | 800ml |
| Privigen 10%, Octagam 10%, Intratect 10%, Flebogamma 10% | 200ml | 400ml |

*Due to the slight variability between the products and batches, the lowest antibody levels found have been used to calculate the doses of intravenous immunoglobulin required to achieve the recommended dose of anti-tetanus antibodies.

Please note that intravenous immunoglobulin (IVIG) is not available from Public Health England (PHE). Healthcare Trusts should contact Manufacturers directly for supply (see Appendix).

# Appendix: Results from Tetanus Antitoxin assays for Human Normal Immunoglobulin

Testing of human normal immunoglobulin products Subgam and Viagam for levels of tetanus antibodies was performed at the National Institute for Biological Standards and Control (NIBSC) in 2008 and 2011. In 2016, NIBSC undertook further testing of Subgam (for subcutaneous or IM use) and eight IVIG products commonly in use in the NHS: Vigam 5%, Gammaplex 5%, Privigen 10%, Octagam 10%, Intratect (5% & 10%) and Flebogama (5% and 10%). All products tested were comparable in terms of tetanus potency. The 5% products have a tetanus potency of approx. 15 IU/ml and the 10% products of approximately 30 IU/ml. Due to the slight variability between the products and batches, the lowest antibody levels found have been used to calculate the doses of human normal immunoglobulin required to achieve the recommended dose of tetanus antibodies.

| Year of test | Product | Manufacturer | Route | Batch number | ELISA IU/ml (95% ci) | TNT assay IU/ml |
|---|---|---|---|---|---|---|
| 2008 | Subgam | BPL | SC/IM | SCBN7647 | 63 | 57 (48-69) |
| 2008 | Subgam | BPL | SC/IM | SCBN7651 | 64 | 57 (48-69) |
| 2011 | Subgam (750mg) | BPL | SC/IM | SCBN8611 | 66.4 | |
| 2011 | Subgam (750mg) | BPL | SC/IM | SCBN8949 | 56.9 | |
| 2011 | Subgam (1500mg) | BPL | SC/IM | SCAN9129 | 60.8 | |
| 2008 | Vigam | BPL | IV | VLAN7724 | 23 | 26 (18-46) |
| 2008 | Vigam | BPL | IV | VLAN7759 | 20 | 18 (15-22) |
| 2008 | Vigam | BPL | IV | VLAN7730 | 23 | 21 (18-26) |
| 2011 | Vigam (5g) | BPL | IV | VLCN9116 | 17.5 | |
| 2011 | Vigam (5g) | BPL | IV | VLCN9117 | 17.9 | |
| 2011 | Vigam (10g) | BPL | IV | VLAN9219 | 15.9 | |
| 2011 | Vigam (10g) | BPL | IV | VLAN9220 | 15.9 | |
| 2016 | Vigam 5% | BPL | IV | VLA15350<br>VLA15015<br>VLAN0825 | 15.3 (14.5-16.2)<br>16.7 (15.8-17.6)<br>17.6 (16.7-18.6) | 21.0 (17.8-25.4) |
| 2011 | Gammaplex (5g) | BPL | IV | VSCN8627 | 17.8 | |
| 2011 | Gammaplex (5g) | BPL | IV | VSCN9016 | 17.2 | |
| 2011 | Gammaplex (5g) | BPL | IV | VSCN9156 | 19.6 | |
| 2011 | Gammaplex (10g) | BPL | IV | VSAN8599 | 21.6 | |
| 2011 | Gammaplex (10g) | BPL | IV | VSAN9070 | 16.7 | |

| Year of test | Product | Manufacturer | Route | Batch number | ELISA IU/ml (95% ci) | TNT assay IU/ml |
|---|---|---|---|---|---|---|
| 2011 | Gammaplex (10g) | BPL | IV | VSAN9083 | 17.6 | |
| 2016 | Gammaplex 5% | BPL | IV | VSB15360<br>VSA15074<br>VSA15278 | 15.0 (14.2-15.9)<br>16.6 (15.7-17.6)<br>14.7 (13.9-15.6) | 19.8(16.8-24.0) |
| 2016 | Privigen 10% | CSL | IV | 432900015 | 27.7 (26.0-29.5) | 32.6 (27.7-39.5) |
| 2016 | Octagam 10% | Octapharma | IV | L609A8541<br>A436B854E<br>A550B8542 | 30.1 (28.2-32.0)<br>34.3 (32.2-36.6)<br>31.2 (29.5-33.0) | 39.6 (33.7-47.9) |
| 2016 | Intratect 10% | Biotest | IV | B790035 8<br>B790035 6<br>B790016 02<br>B790155 7 | 24.0 (22.8-25.4)<br>25.8 (24.5-27.3)<br>30.7 (28.5-33.2)<br>28.2 (26.2-30.5) | 27.9 (23.8-33.8) |
| 2016 | Intratect 5% | Biotest | IV | B791275 6<br>B791405 13<br>B791615 6<br>B791415 4 | 15.7 (14.6-16.9)<br>14.6 (14.0-15.3)<br>15.4 (14.7-16.1)<br>14.5 (13.8-15.1) | |
| 2016 | Flebogamma 10% | Grifols | IV | IBGP4JNJP1<br>IGGP5B6001<br>IBGN4DIDK1 | 29.3 (27.5-31.2)<br>32.1 (30.2-34.2)<br>31.4 (29.5-33.4) | 36.1 (30.7-43.7) |
| 2016 | Flebogamma 5% | Grifols | IV | IBGL5DCDE1<br>IBGK4EPES1<br>IBGJ5R4R61 | 14.8 (14.0-15.6)<br>16.3 (15.5-17.2)<br>15.6 (14.8-16.4) | |

Manufacturers' contact details:
BPL (Bio Products Laboratory) Tel: 020 8258 2200
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CSL Behring 01334 447400
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