



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 be 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	
<p>Those aged 11 years and over, who have received an adequate priming course of tetanus vaccine¹ with the last dose within 10 years</p> <p>Children under 5 years who have received an adequate priming course</p>	None required	None required	None required	Further doses as required to complete the recommended schedule (to ensure future immunity)
<p>Received adequate priming course of tetanus vaccine¹ but last dose more than 10 years ago</p> <p>Children aged 5-10 years who have received an adequate priming course but no preschool booster</p> <p><i>Includes UK born after 1961 with history of accepting vaccinations</i></p>	None required	Immediate reinforcing dose of vaccine	<p>Immediate reinforcing dose of vaccine</p> <p>One dose of human tetanus immunoglobulin² in a different site</p>	Further doses as required to complete the recommended schedule (to ensure future immunity)
<p>Not received adequate priming course of tetanus g vaccine¹</p> <p><i>Includes uncertain immunisation status and/or born before 1961</i></p>	Immediate reinforcing dose of vaccine	<p>Immediate reinforcing dose of vaccine</p> <p>One dose of human tetanus immunoglobulin¹ in a different site</p>	<p>Immediate reinforcing dose of vaccine</p> <p>One dose of human tetanus immunoglobulin² in a different site</p>	

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-Tlg	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
Gammaflex 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 VLA15015 VLAN0825	15.3 (14.5-16.2) 16.7 (15.8-17.6) 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	

Recommendations on the treatment and prophylaxis of tetanus

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 VSA15074 VSA15278	15.0 (14.2-15.9) 16.6 (15.7-17.6) 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 A436B854E A550B8542	30.1 (28.2-32.0) 34.3 (32.2-36.6) 31.2 (29.5-33.0)	39.6 (33.7-47.9)
2016	Intratect 10%	Biotest	IV	B790035 8 B790035 6 B790016 02 B790155 7	24.0 (22.8-25.4) 25.8 (24.5-27.3) 30.7 (28.5-33.2) 28.2 (26.2-30.5)	27.9 (23.8-33.8)
2016	Intratect 5%	Biotest	IV	B791275 6 B791405 13 B791615 6 B791415 4	15.7 (14.6-16.9) 14.6 (14.0-15.3) 15.4 (14.7-16.1) 14.5 (13.8-15.1)	
2016	Flebogamma 10%	Grifols	IV	IBGP4JNJP1 IGGP5B6001 IBGN4DIDK1	29.3 (27.5-31.2) 32.1 (30.2-34.2) 31.4 (29.5-33.4)	36.1 (30.7-43.7)
2016	Flebogamma 5%	Grifols	IV	IBGL5DCDE1 IBGK4EPES1 IBGJ5R4R61	14.8 (14.0-15.6) 16.3 (15.5-17.2) 15.6 (14.8-16.4)	

Manufacturers' contact details:

BPL (Bio Products Laboratory) Tel: 020 8258 2200

Grifols UK Ltd Tel: 0 845 2413090

Biotest Uk Ltd Tel: 0121 733 3393

CSL Behring 01334 447400

Octapharma 0161 837 3771