

Table 1: Immune responses to diphtheria, tetanus and acellular pertussis components following booster vaccination in adults and adolescents above 10 years of age

Age at booster	Previous Vaccinations	Results following vaccination with dTpa (N)				
		anti-PT*	anti-FHA*	anti-PRN*	anti-diphtheria †	anti-tetanus†
10-13 years	4 doses DTPw (primary plus booster)	92.1% (441)	96.8% (447)	98.9% (447)	100% (447)	100% (447)
11-17 years	4 doses DTPw (primary plus booster)	100% (40)	95.0% (40)	100% (40)	100% (40)	100% (40)
≥ 18 years**	Variable vaccination histories	95.0% (522)	99.2% (520)	98.5% (522)	92.7% (519)	99.8% (523)

† Percentage of vaccinees having anti-diphtheria and anti-tetanus antibody titres ≥ 0.1 IU/ml post-vaccination

* Percentage of vaccinees having anti-PT, anti-FHA, anti-PRN antibody titres ≥ cut-off (i.e., 5 EU/ml) post-vaccination for initially seronegative subjects; or the percentage of vaccinees having a 2-fold increase in anti-PT, anti-FHA, anti-PRN antibody titres post-vaccination for initially seropositive subjects

** Pooled results from two pivotal studies in adults

N= number of subjects.

Results of the comparative studies with commercial dT vaccines indicates that the degree and duration of protection would not be different from those obtained with these vaccines.

The GMT values for the three pertussis antigens following a booster dose of BOOSTRIX to adolescents and adults are provided in tables 2 and 3:

Table 2: GMT values for pertussis antigens after vaccination of adolescents between 10 and 13 years of age with BOOSTRIX

Antigen	10-13 years of age (N for post-booster*)	GMT (EI.U/mL) pre-booster	GMT (EI.U/mL) post-booster#
PT	441	9.7	117.6
FHA	447	58.3	923.3
PRN	447	17.5	594.8

One month after vaccination

* The number of subjects included in the pre-booster analysis differs

Table 3: GMT values for pertussis antigens after vaccination of adults with BOOSTRIX

Antigen	≥ 19 years of age (N for post-booster*)	GMT (EI.U/mL) pre-booster	GMT (EI.U/mL) post-booster#
PT	427	8.8	88.1
FHA	426	40.6	1178.9
PRN	427	11.0	472.8

One month after vaccination

* The number of subjects included in the pre-booster analysis differs

A pooled analysis of the Immune response results to the diphtheria, tetanus and acellular pertussis components from 11 comparative and noncomparative clinical studies are presented in table 4 below. Approximately one month following booster vaccination with BOOSTRIX, the following seroprotection / seropositivity rates were observed:

Table 4: Pooled analysis of immune responses to diphtheria, tetanus and acellular pertussis components following booster vaccination in adults and adolescents above 10 years of age (at least 1670 subjects)

Antigen	Response ⁽¹⁾		% Vaccinees (CI)	GMC (CI)
Diphtheria	≥0.1 IU/mL	Pre	68.4% (66.1-70.6)	0.274 (0.166-0.451)
		Post	97.2% (96.3-97.9)	3.382 (2.184-5.235)
Tetanus	≥0.1 IU/mL	Pre	88.6% (87.0-90.0)	0.654 (0.418-1.024)
		Post	99.0% (98.4-99.4)	8.491 (5.632-12.801)
Pertussis <i>Pertussis toxoid</i>	≥5 EL.U/mL	Pre	56.9% (54.5-59.3)	7.3 (5.9-9.0)
		Post	97.8% (96.9-98.4)	85.2 (69.8-104.0)
Filamentous haemagglutinin	≥5 EL.U/mL	Pre	96.9% (96.0-97.7)	35.3 (28.9-43.2)
		Post	99.9% (99.7-100)	830.9 (725.6-951.5)
Pertactin	≥5 EL.U/mL	Pre	70.1% (67.8-72.3)	11.4 (8.7-14.8)
		Post	99.4% (98.9-99.7)	480.0 (342.8-672.1)

⁽¹⁾Response: Where at the specified time point, a concentration of antibodies against diphtheria and tetanus ≥0.1 IU/mL was considered as seroprotection and a concentration of antibodies against pertussis ≥5 EL.U/mL was considered as seropositivity

% Vaccinees = percentage of subjects with concentration within the specified range

GMC = geometric mean antibody concentration calculated on all subjects

CI = Confidence interval (95%)

Pre = blood sample taken prior to booster vaccination

Post = blood sample taken approximately one month after booster vaccination

Protective efficacy of pertussis

There is currently no correlate of protection defined for pertussis; however, the protective efficacy of GlaxoSmithKline Biologicals' DTPa (INFANRIX[®]) vaccine against WHO-defined typical pertussis (≥ 21 days of paroxysmal cough with laboratory confirmation) was demonstrated in the following 3-dose primary studies:

- a prospective blinded household contact study performed in Germany (3, 4, 5 months schedule).

Based on data collected from secondary contacts in households where there was an index case with typical pertussis, the protective efficacy of the vaccine was 88.7%. Protection against laboratory confirmed mild disease, defined as 14 days or more of cough of any type was 73% and 67% when defined as 7 days or more of cough of any type.

- an NIH sponsored efficacy study performed in Italy (2, 4, 6 months schedule).

The vaccine efficacy was found to be 84%. When the definition of pertussis was expanded to include clinically milder cases with respect to type and duration of cough, the efficacy of INFANRIX[®] was calculated to be 71% against >7 days of any cough and 73% against >14 days of any cough. In a follow-up of the same cohort, the efficacy was confirmed up to 5

years after completion of primary vaccination without administration of a booster dose of pertussis.

The study assessed duration of protection of Infanrix given in a 3 dose schedule to infants. A similar duration of protection cannot be assumed to apply to older children or adults given a single dose of BOOSTRIX, regardless of previous vaccination against pertussis.

Although the protective efficacy of BOOSTRIX has not been demonstrated in adolescents and adult age groups, vaccinees in these age groups who received BOOSTRIX achieved anti-pertussis antibody titres greater than those in the German household contact study where the protective efficacy of Infanrix was 88.7%.

There are currently no data which demonstrate a reduction of transmission of pertussis after immunisation with BOOSTRIX. However, it could be expected that immunisation of immediate close contacts of newborn infants, such as parents, grandparents and healthcare workers, childcare workers, would reduce exposure of pertussis to infants not yet adequately protected through immunisation.

Persistence of immunity to diphtheria, tetanus and pertussis after vaccination with BOOSTRIX in adolescents and adults

The following responses for diphtheria, tetanus and pertussis were observed 3 to 3.5 years, 5 years and 10 years following vaccination with BOOSTRIX in adolescents (Table5) and adults (Table6):

Table 5: Data on persistence up to 3-3.5 years (study dTpa-017), 5 years (study dTpa-030) and 10 years (study dTpa-040) after vaccination of adolescents between 10 and 13 years of age with BOOSTRIX in study dTpa-004 (ATP¹)

Antigen	Response ²	Adolescents ³ % Vaccines (CI)		
		3-3.5 years persistence	5 years persistence	10 years persistence
Diphtheria	≥ 0.1 IU/mL ⁴	91.6% (87.6 – 94.7)	86.8% (82.0-90.7)	82.4% (71.8-90.3)
	≥ 0.016 IU/mL ⁴	100% (98.2-100)	99.2% (96.9-99.9)	98.6% (92.7-100)
Tetanus	≥ 0.1 IU/mL	100% (98.6-100)	100% (98.6-100)	97.3% (90.6-99.7)
Pertussis				
Pertussis toxoid	≥ 5 EL.U/mL	81.6% (76.4-86.1)	76.8% (71.1-81.9)	61.3% (49.4-72.4)
Filamentous haemagglutinin	≥ 5 EL.U/mL	100% (98.6-100)	100% (98.6-100)	100% (95.2-100)
Pertactin	≥ 5 EL.U/mL	99.2% (97.3-99.9)	98.1% (95.5-99.4)	96.0% (88.8-99.2)

⁽¹⁾ ATP: According to protocol – includes all eligible participants, who had received a single booster dose of BOOSTRIX, for whom immunogenicity data was available for at least one antigen at the specified time-point.

⁽²⁾ Response: Where, at the specified time point, a concentration of antibodies against diphtheria and tetanus ≥ 0.1 IU/mL was considered as seroprotection and a concentration of antibodies against pertussis ≥ 5 EL.U/mL was considered as seropositivity

⁽³⁾ The term ‘adolescents’ reflects the age at which the participants received their first vaccination with BOOSTRIX

⁽⁴⁾ Percentage of participants with antibody concentrations associated with protection against disease (≥ 0.1 IU/mL by ELISA assay or ≥ 0.016 IU/mL by an in-vitro Vero-cell neutralisation assay).

CI = Confidence Interval (95%)

Table 6: Data on persistence up to 3-3.5 years (study dTpa-021), 5 years (study dTpa-027) and 10 years (study dTpa-039) after vaccination of adults between 19 and 70 years of age with BOOSTRIX in study dTpa-002 (ATP¹)

Antigen	Response ²	Adults ³ % Vaccines (CI)		
		3-3.5 years persistence	5 years persistence	10 years persistence
Diphtheria	≥ 0.1 IU/mL ⁴	71.2% (65.8-76.2)	84.1% (78.7-88.5)	64.6% (56.6-72.0)
	≥ 0.016 IU/mL ⁴	97.4% (95.6-99.2)	94.4% (90.6-97.0)	89.9% (84.1-94.1)
Tetanus	≥ 0.1 IU/mL	94.8% (91.8-97.0)	96.2% (93.0-98.3)	95.0% (90.4-97.8)
Pertussis				
Pertussis toxoid	≥ 5 EL.U/mL	90.6% (86.8-93.6)	89.5% (84.9-93.1)	85.6% (79.2-90.7)
Filamentous haemagglutinin	≥ 5 EL.U/mL	100% (98.8-100)	100% (98.5-100)	99.4% (96.6-100)
Pertactin	≥ 5 EL.U/mL	94.8% (91.7-97.0)	95.0% (91.4-97.4)	95.0% (90.3-97.8)

⁽¹⁾ ATP: According to protocol – includes all eligible participants, who had received a single booster dose of BOOSTRIX, for whom immunogenicity data was available for at least one antigen at the specified time-point.

⁽²⁾ Response: Where, at the specified time point, a concentration of antibodies against diphtheria and tetanus ≥ 0.1 IU/mL was considered as seroprotection and a concentration of antibodies against pertussis ≥ 5 EL.U/mL was considered as seropositivity

⁽³⁾ The term ‘adults’ reflects the age at which the participants received their first vaccination with BOOSTRIX

⁽⁴⁾ Percentage of participants with antibody concentrations associated with protection against disease (≥ 0.1 IU/mL by ELISA assay or ≥ 0.016 IU/mL by an in-vitro Vero-cell neutralisation assay).

CI = Confidence Interval (95%)

BOOSTRIX administered in subjects ≥40 years of age with an incomplete, unknown or no history of a primary series of diphtheria and tetanus toxoid vaccination history induced an antibody response against pertussis in more than 98.5% of adults and provided seroprotection against diphtheria and tetanus in 81.5% and 93.4% of adults respectively.

Two subsequent doses maximised the vaccine response against diphtheria and tetanus when administered at one and six months (99.3% and 100% respectively).

Vaccination with second dose of BOOSTRIX

The immunogenicity of BOOSTRIX, administered 10 years after a previous booster dose with BOOSTRIX or reduced-antigen content diphtheria, tetanus and acellular pertussis vaccines has been evaluated in adults. One month after the decennial BOOSTRIX dose, >99 % of subjects were seroprotected against diphtheria and tetanus and all were seropositive for antibodies against pertussis antigens PT, FHA and PRN.

INDICATIONS

BOOSTRIX is indicated for booster vaccination against diphtheria, tetanus and pertussis of individuals aged ten years and older.

CONTRAINDICATIONS

BOOSTRIX should not be administered to subjects with known hypersensitivity to any component of the vaccine, or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus or pertussis vaccines.

As with other vaccines, the administration of BOOSTRIX should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, is not a contraindication.

BOOSTRIX is contra-indicated if the subject has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis-containing vaccine. In these circumstances, pertussis vaccination should be discontinued and the vaccination course should be continued with diphtheria and tetanus vaccines.

BOOSTRIX should not be administered to subjects who have experienced transient thrombocytopenia or neurological complications following an earlier immunisation against diphtheria and/or tetanus (for convulsions or hypotonic-hyporesponsive episodes, see PRECAUTIONS).

PRECAUTIONS

BOOSTRIX should under no circumstances be administered intravenously.

It is good clinical practice that immunisation should be preceded by a review of the medical history (especially with regard to previous immunisation and possible occurrence of undesirable events) and a clinical examination.

If any of the following events have occurred in temporal relation to receipt of pertussis containing vaccines, the decision to give doses of pertussis containing vaccines, should be carefully considered.

There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks, particularly since these events are not associated with permanent sequelae.

- Temperature of $\geq 40.0^{\circ}\text{C}$ within 48 hours of vaccination, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.

- Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours of vaccination.
- Convulsions with or without fever, occurring within 3 days of vaccination.

In children with progressive neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy, it is better to defer pertussis (Pa or Pw) immunisation until the condition is corrected or stable. However, the decision to give pertussis vaccine must be made on an individual basis after careful consideration of the risks and benefits.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of anaphylactic reactions following the administration of the vaccine.

BOOSTRIX should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects. Firm pressure should be applied to the injection site (without rubbing) for at least two minutes.

A history or a family history of convulsions and a family history of an adverse event following DTP vaccination do not constitute contra-indications.

Human Immunodeficiency Virus (HIV) infection is not considered a contraindication for diphtheria, tetanus and pertussis (whole-cell or acellular) immunisation. However in patients with immunodeficiency or in patients receiving immunosuppressive therapy, an adequate immunologic response may not be achieved. In these patients, when tetanus vaccine is needed for tetanus prone wound, plain tetanus vaccine should be used.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

Effects on fertility

No human data are available. In combined fertility and embryofetal development studies in rats and rabbits, female fertility was unaffected by IM administration of BOOSTRIX twice before mating with 2/5x (rats) or 1x (rabbits) the human dose.

Use in Pregnancy (Category B1)

Combined embryofetal development studies in which rats or rabbits were IM administered BOOSTRIX twice before mating and several times during gestation (and once during lactation in rats) with 2/5x (rats) or 1x (rabbits) the human dose showed no effects on embryofetal development, nor on postnatal development in rats.

As with all inactivated vaccines, one does not expect harm to the fetus.

However, adequate human data on use during pregnancy are not available. Therefore, BOOSTRIX should be used during pregnancy only when clearly needed, and the possible advantages outweigh the possible risks for the fetus. When protection against tetanus is sought, consideration should be given to tetanus or combined diphtheria-tetanus vaccines.

Use in Lactation

The safety of BOOSTRIX when administered to breast-feeding women has not been evaluated.

It is unknown whether BOOSTRIX is excreted in human breast milk.

BOOSTRIX should only be used during breast-feeding when the possible advantages outweigh the potential risks.

Genotoxicity

BOOSTRIX has not been evaluated for genotoxicity.

Carcinogenicity

BOOSTRIX has not been evaluated for carcinogenicity.

Effects on the ability to drive and use machines

The vaccine is unlikely to produce an effect on the ability to drive and use machines.

INTERACTIONS WITH OTHER MEDICINES

Concomitant use with other inactivated vaccines and with immunoglobulin is unlikely to result in interference with the immune responses.

If BOOSTRIX is to be given at the same time as another injectable vaccine or immunoglobulin, the products should always be administered at different sites.

BOOSTRIX must not be mixed with other vaccines.

ADVERSE REACTIONS

Clinical Trial Experience

The safety profile below is based on data from clinical trials where BOOSTRIX was administered to 1931 adults, adolescents and children (above 10 years of age). Data from clinical trials conducted for BOOSTRIX in 839 children (from 4 to 9 years of age) is also provided.

The adverse reactions are listed within body systems and are listed according to the following frequency:

- Very common: $\geq 1/10$
- Common: $\geq 1/100$ and $< 1/10$
- Uncommon: $\geq 1/1000$ and $< 1/100$
- Rare: $\geq 1/10,000$ and $< 1/1000$
- Very rare: $< 1/10,000$

Adults, adolescents and children from the age of 10 years onwards

Infections and infestations

Uncommon: upper respiratory tract infection, pharyngitis

Blood and lymphatic system disorders

Uncommon: lymphadenopathy

Nervous system disorders

Very common: headache

Common: dizziness

Uncommon: syncope

Respiratory, thoracic and mediastinal disorders

Uncommon: cough

Gastrointestinal disorders

Common: nausea, gastrointestinal disorders

Uncommon: diarrhoea, vomiting

Skin and subcutaneous tissue disorders

Uncommon: hyperhidrosis, pruritus, rash

Musculoskeletal and connective tissue disorders

Uncommon: arthralgia, myalgia, joint stiffness, musculoskeletal stiffness

General disorders and administration site conditions

Very common: injection site reactions (including pain, redness and swelling), fatigue, malaise

Common: fever ≥ 37.5 °C, injection site reactions (such as injection site mass and injection site abscess sterile)

Uncommon: fever > 39 °C, influenza like illness, pain

Data on 146 subjects suggest a small increase in local reactogenicity (pain, redness, swelling) with repeated vaccination according to a 0, 1, 6 months schedule in adults (>40 years of age).

Subjects fully primed with 4 doses of DTPw followed by BOOSTRIX dose around 10 years of age show an increase of local reactogenicity after an additional BOOSTRIX dose administered 10 years later compared to after the first BOOSTRIX dose.

Children from 4 to 9 years of age

Infections and infestations

Uncommon: upper respiratory tract infection

Metabolism and nutrition disorders

Common: anorexia

Psychiatric disorders

Very common: irritability

Nervous system disorders

Very common: somnolence

Common: headache

Uncommon: disturbances in attention

Eye disorders

Uncommon: conjunctivitis

Gastrointestinal disorders

Common: diarrhoea, vomiting, gastrointestinal disorders

Skin and subcutaneous tissue disorders

Uncommon: rash

General disorders and administration site conditions

Very common: injection site reactions (including pain, redness and swelling), fatigue

Common: fever ≥ 37.5 °C (including fever > 39 °C),

Uncommon: other injection site reactions (such as induration), pain

Post-marketing experience

Extremely rare cases of collapse or shock-like state (hypotonic-hyporesponsiveness episode) and convulsions within 2 to 3 days of vaccination have been reported following DTPa and DTPa combination vaccines.

Blood and lymphatic system disorders

Rare: angioedema

Immune system disorders

Very rare: allergic reactions, including anaphylactic and anaphylactoid reactions

Nervous system disorders

Rare: convulsions (with or without fever)

Skin and subcutaneous tissue disorders

Rare: urticaria

General disorders and administration site conditions

Rare: extensive swelling of the vaccinated limb, asthenia

DOSAGE AND ADMINISTRATION

All parenteral drug and vaccine products should be inspected visually for any particulate matter or discolouration prior to administration. Before use of BOOSTRIX, the vaccine should be well shaken to obtain a homogenous turbid suspension. Discard the vaccine if it appears otherwise.

Dosage

Each dose consists of a 0.5mL ready to use sterile suspension.

Administration

BOOSTRIX is administered by deep intramuscular injection, preferably in the deltoid region. THE VACCINE SHOULD NEVER BE ADMINISTERED INTRAVENOUSLY.

BOOSTRIX should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects. Firm pressure should be applied to the injection site (without rubbing) for at least two minutes.

This product is for use by one patient on a single occasion.

Any unused product or waste material should be disposed of in accordance with local requirements.

BOOSTRIX can be given in accordance with current local recommendations for booster vaccination with adult-type combined diphtheria-tetanus vaccine, when a booster against pertussis is desired.

Individuals with an incomplete, or no, history of a primary series of diphtheria and tetanus toxoids should not be vaccinated with BOOSTRIX. BOOSTRIX is not precluded in subjects

with an incomplete, or no, history of previous pertussis vaccination. However, a booster response will only be elicited in individuals who have been previously primed by vaccination or by natural infection.

Tetanus-prone injury:- In case of tetanus-prone injury, BOOSTRIX can be used as an alternative to adult-type combined diphtheria–tetanus in individuals with no history of tetanus toxoid within the preceding five years, if a booster against diphtheria and pertussis is additionally desired.

BOOSTRIX can be used as an alternative to diphtheria-tetanus in the management of tetanus prone injuries in persons who have previously received a primary vaccination series of tetanus toxoid vaccine. If required, tetanus immunoglobulin may be administered concomitantly in accordance with official recommendations.

OVERDOSAGE

Cases of overdose have been reported during post-marketing surveillance. Adverse events following overdose, when reported, were similar to those reported with normal vaccine administration.

PRESENTATION AND STORAGE CONDITIONS

Storage

BOOSTRIX should be stored at +2°C and +8°C. DO NOT FREEZE; discard if vaccine has been frozen. The expiry date of the vaccine is indicated on the label and packaging.

Presentations

BOOSTRIX is presented as a turbid white suspension in a glass vial or glass prefilled syringe. Upon storage a white deposit and clear supernatant can be observed.

This is a normal finding.

The vials and prefilled syringes are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements.

Not all pack sizes and presentations maybe marketed.

NAME AND ADDRESS OF THE SPONSOR

Manufacturer:

GlaxoSmithKline Biologicals SA
rue de l'Institut 89

1330 Rixensart, Belgium.

Distributed in Australia by:

GlaxoSmithKline Australia Pty Ltd
Level 4,
436 Johnston Street,
Abbotsford, Victoria, 3067

POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 20 April 2009

DATE OF MOST RECENT AMENDMENT: 5 August 2014

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