Guidance for use of Tdap in adults aged 65 years and older

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Td515: Safety and immunogenicity of Adacel vs. Td in persons ≥65 years of age

- Active-controlled, randomized, modified double-blind trial conducted at 19 sites in the US
- Participants randomized in a 3:1 ratio to receive a single dose of Adacel vaccine or DECAVAC® (Td Adsorbed) vaccine
- Overall, 1/3 of the study subjects were ≥ 75 years of age, and 2/3 were 65-74 years of age

Study Vaccine Recipients by Age Group

Vaccine	65 – 74 years	≥ 75 years	Total
Adacel	780	390	1170
DECAVAC (Td)	262	129	391
Total	1042	519	1561

Adacel in persons ≥ 65 years of age: summary of safety and tetanus and diphtheria immunogenicity

- **Safety**
  - Rates of local and systemic reactions did not differ with Td
- **Immunogenicity (tetanus and diphtheria)**
  - Antibody responses similar to Td
  - Non-inferiority criteria met

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Postvaccination pertussis antibody GMCs for Adacel and 3 or 4 doses* Daptacel

	Daptacel (Infants, 3- or 4-doses*)	Adacel (65+, 1 dose)
Anti-PT	98.1*	59.4
Anti-FHA	39.9	197
Anti-PRN	108	69.2
Anti-FIM	341.1	183

* Comparison for PT is 4 doses Daptacel; for FHA, PRN, FIM is 3 doses Daptacel

Adapted from data provided by sanofi pasteur

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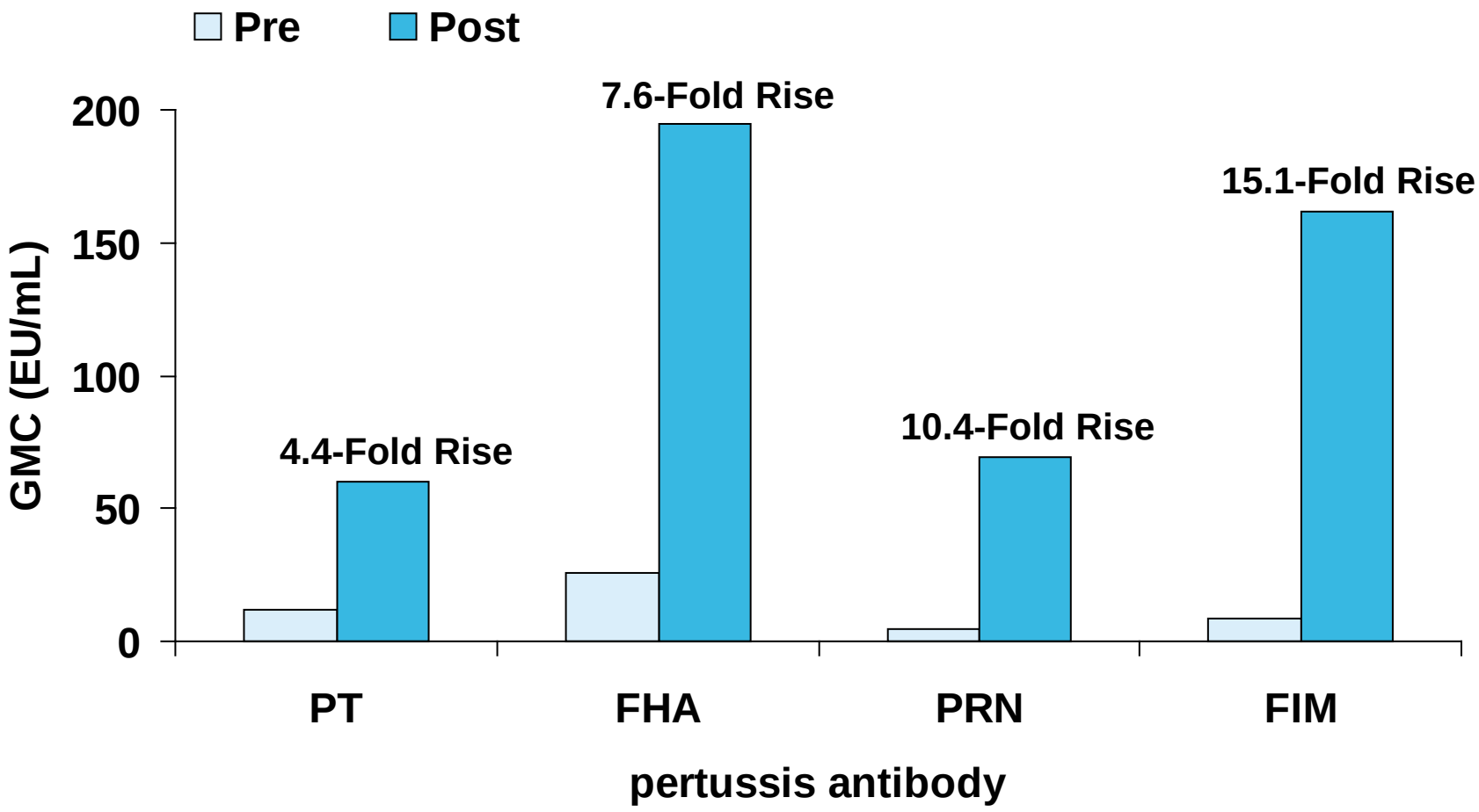
Adacel: Pertussis immunogenicity in adults aged 65 years and older



Pre- and post-immunization GMC for Adacel and Boostrix in adults aged 65 years and older

Adacel (sanofi pasteur)		
GMCs	Pre	Post
PT	11.7	59.8
FHA	25.5	195
PRN	4.6	69.5
FIM	8.7	182

Boostrix (GSK)		
GMCs	Pre	Post
PT	6.6	49.1
FHA	50.2	689.0
PRN	8.1	104.2
FIM	-	-

For hypothesis generation only

GMC = Geometric Mean Concentrations (EU/mL)
Adapted from slide provided by sanofi pasteur

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ACIP WG conclusions: Adacel in adults aged 65 years and older

- Acceptable safety profile
- Pertussis - immunogenic and likely provides protection
- Guidance for use of Adacel in older adults is needed

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Adacel licensure in other jurisdictions

- Canada (country of origin)
  - Ages 4 and up (August 2011)
- European Union – Adacel (Covaxis)
  - German license: 4 years of age and older (March 2006)
  - 28 EU member states: 4 years of age and older (December 2009)
- Australia (2005) & New Zealand (2007)
  - Ages 10 years and up (November 2005)
- Most Latin American and Asian countries follow license in the country of origin (Canada)

GUIDANCE FOR USE OF TDAP IN OLDER ADULTS

Licensed Tdap vaccines

	BOOSTRIX® (GlaxoSmithKline Biologicals)*	ADACEL™ (sanofi pasteur)†
Age Indication (years)	**10 and older**	**11 through 64**
Usage	**Active booster immunization for prevention of tetanus, diphtheria, and pertussis as a single dose**	

* Product label available at http://us.gsk.com/products/assets/us_boostrix.pdf

† Product label available at http:www.vaccineplace.com/products/

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ACIP guidance on use of Tdap products for adults aged 65 years and older

- When feasible, the approved Tdap vaccine for adults aged 65 years and older should be used.
- A dose of Adacel administered to a person aged 65 years and older is considered valid.
- Providers should not miss an opportunity to vaccinate persons aged 65 years and older with Tdap, and may administer the vaccine that they have available.*

* Phrasing from the General Recommendations Interchangeability language

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DISCUSSION

Proposed recommendation for use of Tdap products in adults aged 65 years and older

- **Option 1:**
  - For Tdap vaccination of adults aged 65 years and older, either Tdap product may be used.

- **Option 2:**
  - For Tdap vaccination of adults aged 65 years and older, Boostrix (GSK) is preferred but either product may be used.

Composition of Tdap vaccines and age for licensed use for persons aged 10 years and older

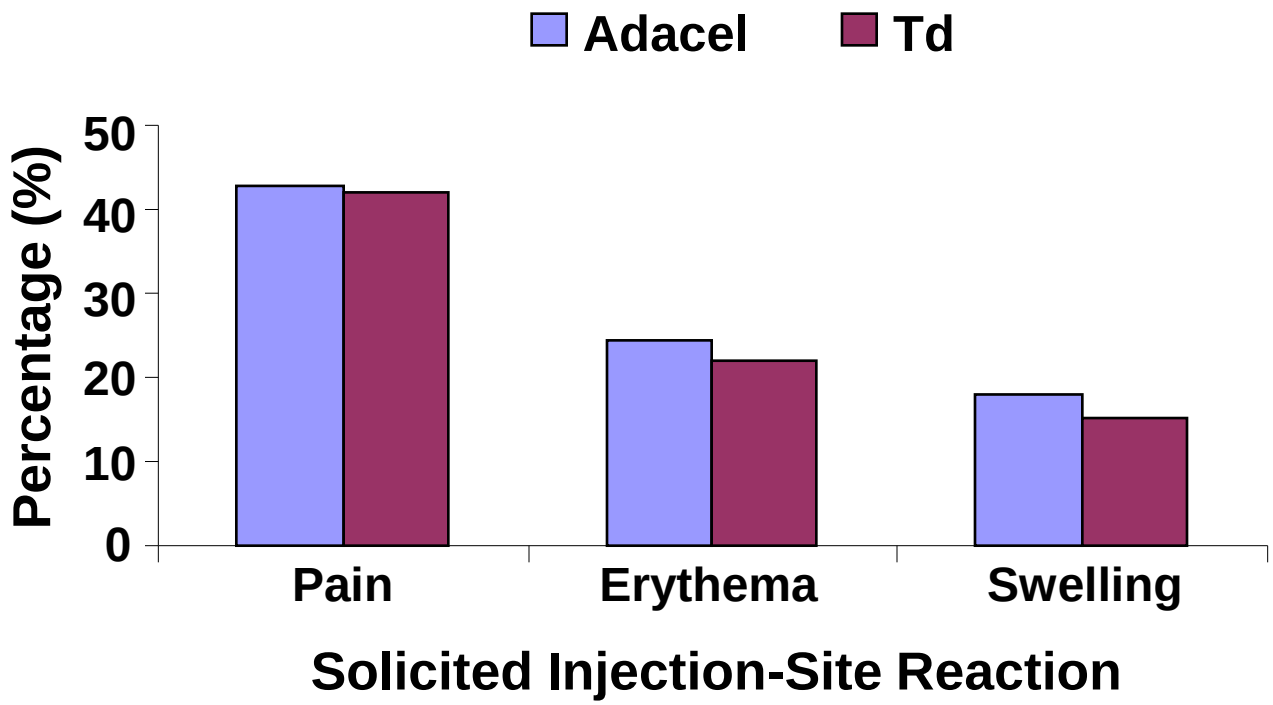
Trade name	Manufacturer	Pertussis antigens (µg)				Diphtheria toxoids (Lf)	Tetanus toxoids (Lf)	Approved age (years)
		PT	FHA	PRN	FIM			
BOOSTRIX	GlaxoSmithKline Biologicals (GSK)	8	8	2.5		2.5	5	10 and older
ADACEL	sanofi pasteur	2.5	5	3	5	2	5	11 – 64*

* A dose of Adacel administered to a person aged 65 years and older is considered valid.

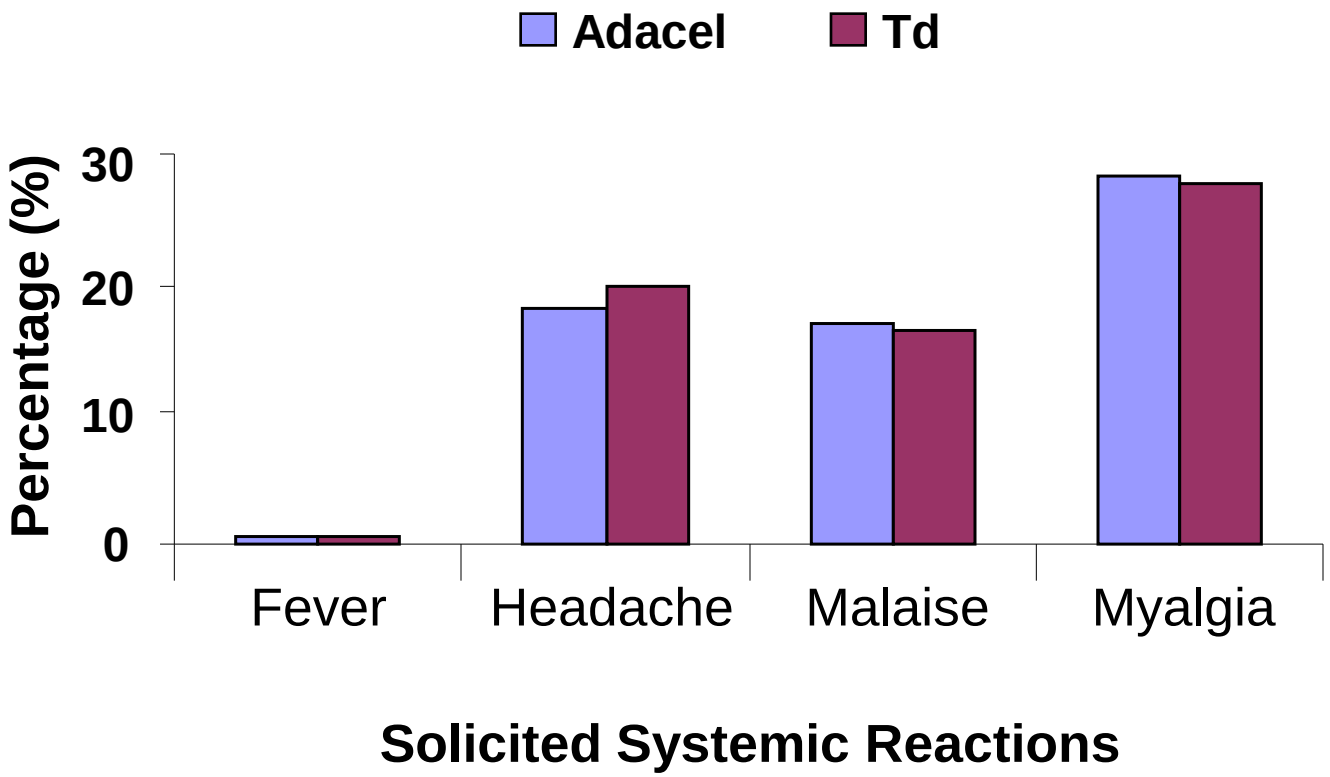
PT- Pertussis toxin; FHA - filamentous haemagglutinin; PRN - pertactin; FIM - fimbriae

ADACEL SLIDES

Td515: Summary of solicited injection-site reactions, days 0 – 14



Td515: Summary of solicited systemic reactions, days 0 – 14



Td515: Tetanus and diphtheria immunogenicity results

Tetanus and Diphtheria Seroprotection Rates (≥ 0.1 IU/mL) for Adacel and Td – Per Protocol Set

Antibody (IU/mL)	Adacel			Td			Adacel − Td	
	n/N	%	95% CI	n/N	%	95% CI	Difference (%)	95% CI
Tetanus	1058/1075	98.4	97.7; 99.2	361/368	98.1	96.7; 99.5	0.32	-1.26; 1.90
Diphtheria	846/1093	77.4	74.9; 79.9	294/371	79.3	75.1; 83.4	-1.84	-6.66; 2.97

Tetanus and Diphtheria Booster Response Rates for Adacel and Td – Per Protocol Set

Antibody (IU/mL)	Adacel			Td			Adacel − Td	
	n/N	%	95% CI	n/N	%	95% CI	Difference (%)	95% CI
Tetanus	822/1071	76.8	74.2; 79.3	282/365	77.3	73.0; 81.6	-0.5	-5.5; 4.5
Diphtheria	770/1091	70.6	67.9; 73.3	244/370	65.9	61.1; 70.8	4.6	-0.9; 10.2

All non-inferiority criteria met

Td515: Tetanus and diphtheria immunogenicity results (continued)

Tetanus and Diphtheria Antibody GMCs - Per Protocol Set

Antibody (IU/mL)	Adacel			Td			Adacel / Td	
	n/N	GMC	95% CI	n/N	GMC	95% CI	Ratio	95% CI
Tetanus	1075/1094	8.43	7.78; 9.14	368/371	7.23	6.23; 8.38	1.17	0.99; 1.37
Diphtheria	1093/1094	0.57	0.49; 0.67	371/371	0.50	0.40; 0.64	1.14	0.84; 1.52

All non-inferiority criteria met

Td515: Pertussis geometric mean antibody concentrations and fold rises

Geometric Mean Fold Rise (GMFR) for Adacel Recipients in Td515 - Per Protocol Analysis Set

Antibody (EU/mL)	Pre-Vaccination			Post-Vaccination		Post / Pre	
	N	GMC	95% CI	GMC	95% CI	GMFR	95% CI
PT	957	11.7	10.8; 12.6	59.8	55.4; 64.5	4.4	4.1; 4.7
FHA	1091	25.5	23.9; 27.1	195	185; 208	7.6	7.1; 8.1
PRN	1090	4.6	4.3; 4.9	69.5	61.8; 78.1	10.4	9.3; 11.5
FIM	1021	8.7	7.8; 9.6	182	162; 204	15.1	13.5; 16.8

Values below LLOQ were imputed to be 0.5 x LLOQ. LLOQ is 3 EU/mL for FHA , and 4 EU/mL for PT, PRN, and FIM.

Robust responses to all pertussis antigens

Td515: Pertussis GMCs, Adacel vs Sweden I or M5A10 (3 or 4 doses Daptacel in infants)

Postvaccination Pertussis Antibody GMCs for Adacel and Comparison Groups – Per Protocol Set

Antibody (EU/mL)	Adacel			Comparison*			Adacel / Comparison	
	n / N	GMC	95% CI	n / N	GMC	95% CI	Ratio	95% CI
PT	1022 / 1094	59.4	55.2; 63.8	366 / 366	98.1	90.9; 105	0.61	0.53; 0.69
FHA	1094 / 1094	197	186; 2089	80 / 80	39.9	34.6; 46.1	4.93	3.95; 6.16
PRN	1094 / 1094	69.2	61.6; 77.9	80 / 80	108	91.4; 128	0.64	0.41; 0.99
FIM	1060 / 1094	183	163; 205	80 / 80	341.1	270; 431	0.54	0.36; 0.81

*** Comparison is 4 doses Daptacel in M5A10 for PT, 3 doses Daptacel in Sweden I for FHA, PRN, FIM**

Serologic correlates of pertussis protection

- **Storsaeter *et al* established correlates of protection in Sweden I efficacy trial (nested household contact study)**
  - **Pre-exposure sera were dichotomized by antibody levels**
  - **Higher antibody levels did not confer further increase in protection**

Pattern of Antibodies (EU/mL)			Protective Efficacy (%)
PT	PRN	FIM	
≥ 5	< 5	< 5	46
Any	< 5	≥ 5	72
Any	≥ 5	< 5	75
Any	≥ 5	≥ 5	85

- **Kohberger *et al* applied model to other studies, including Td515**

Storsaeter J, *et al*. Levels of anti-pertussis antibodies related to protection after household exposure to *Bordetella pertussis*. Vaccine 1998;16(20):1907–1916.

Kohberger RC, *et al*. Prediction of pertussis vaccine efficacy using a correlates of protection model. Vaccine 2008;26:3516–3521

Td515: Pertussis efficacy estimates per Storsaeter-Kohberger model

	Adacel		Td	
	n	Predicted Efficacy %	n	Predicted Efficacy %
All Participants:				
Before vaccination	974	53.2	327	55.4
After vaccination	992	80.0	321	57.7
Predicted efficacy after vaccination, when seronegative for indicated antigen(s) before vaccination				
Negative for:				
PT, FIM, and PRN	112	74.5	34	15.4
PT	222	77.9	69	42.2
FIM	466	78.5	152	47.5
PRN	592	77.6	196	42.5
PT, FIM, or PRN	752	78.9	243	49.6

Td515: Conclusions

- Adacel vaccine's safety profile very similar to that of standard licensed Td vaccine in persons ≥ 65 years of age
- Adacel vaccine's tetanus and diphtheria immunogenicity profiles very similar to those of standard licensed Td vaccine in persons ≥ 65 years of age
- Adacel vaccine's pertussis immunogenicity profiles in persons ≥ 65 years of age:
  - Characterized by robust responses (4.4- to 15.1-fold increases) to all pertussis antigens in the vaccine
  - Due to assay issues and age-related decline in immune responses, did not satisfy FDA-requested non-inferiority criteria
  - Nonetheless, high effectiveness expected based on Storsaeter criteria
- Adacel (and/or Adacel-Polio) is currently approved for persons aged 4 years and older in Canada (country of origin), the EU, Australia and New Zealand.