Boostrix Revaccination Studies at 9-10 Years – Studies 009 & 012

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Boostrix 009 and 012 – Overview

- Boostrix Study 009 and 012 were revaccination studies with Boostrix at 9 and 10 years, respectively
  - Both studies had a control group that received Boostrix for first time

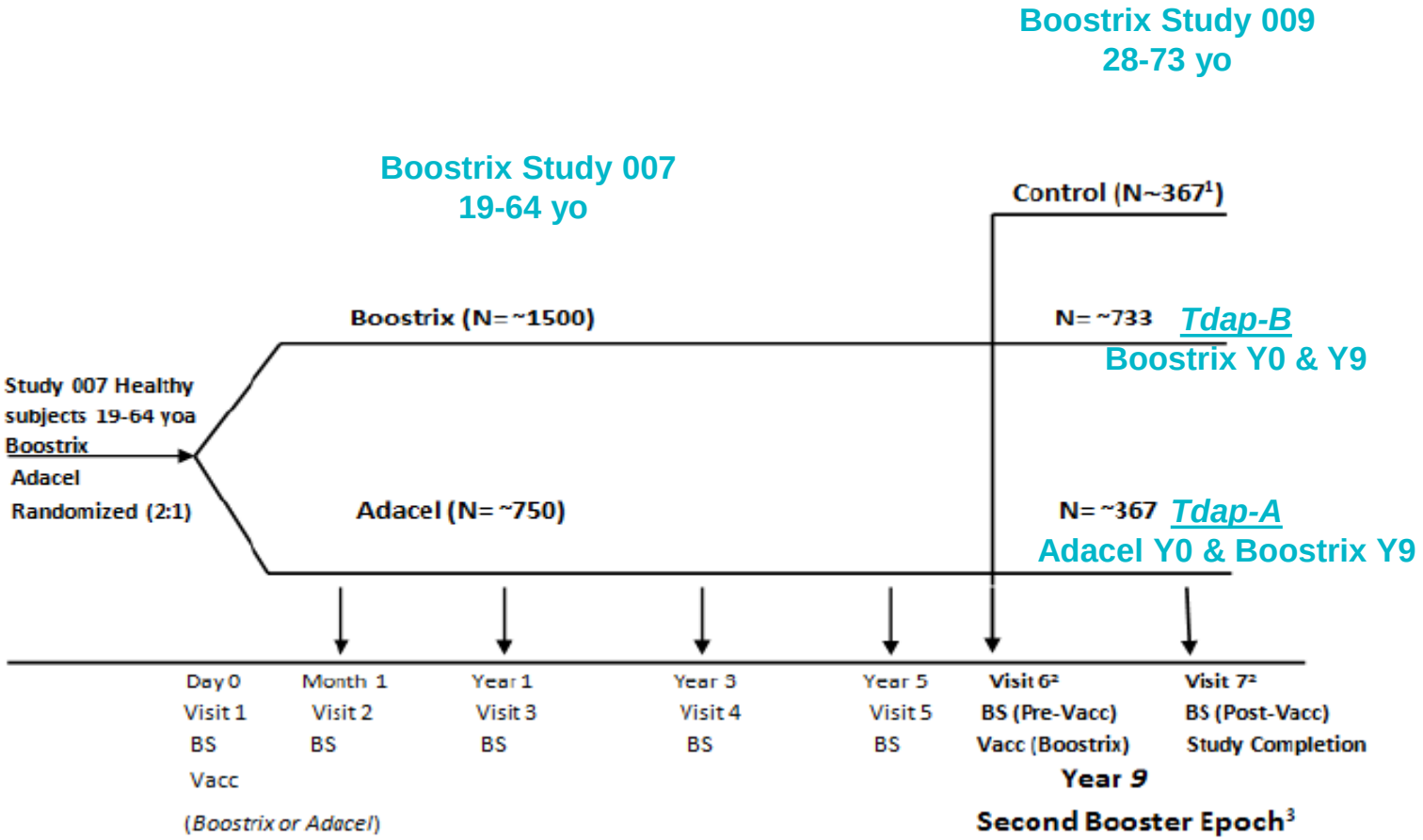
- Both study results met success criteria:
  - Diphtheria and Tetanus - Seroprotection Rates (% ≥ 0.1 IU/mL) for Re-vaccination with Boostrix were Non-Inferior to Vaccination with a First Dose of Boostrix (primary endpoint)
  - PT, PRN and FHA - GMC ratio* (primary endpoint)

- In both studies, groups that received revaccination with Boostrix missed booster response endpoints**; however:
  - Seroprotection rates for Diphtheria & Tetanus of ≥0.1 IU/mL and ≥1.0 IU/mL, respectively, were achieved by
    - > 99% and >91%, of subjects in both studies
  - Pertussis antigen GMC fold-rise pre to post re-vaccination were at least 6-fold in both studies †

- Solicited symptoms (local and general) were generally higher after dose 2 than dose 1, Grade 3 symptoms were similar after dose 1 and dose 2

*Revaccination GMC *divided by* GMC from Infanrix group in German Household Contact Efficacy study
**Booster response was co-primary endpoint in study 009 and secondary endpoint in study012
† Pertussis GMC fold rises for Boostrix Study 009 (groups Tdap-B, Tdap-A) and Study 012 (Tdap), respectively were : PT 7.8, 9.0, 8.8; FHA 5.9, 8.9, 7.9; PRN 6.4, 7.9, 6.5

Boostrix 009* – Study design



A phase III, open-label, interventional, US multicenter study with same two parallel groups as in Boostrix 007 (Boostrix & Adacel) and one new Control group [receiving the first dose of Tdap vaccine (*Boostrix*)].

- Boostrix (Tdap-B) & Adacel (Tdap-A) groups were revaccinated with Boostrix approx. 9 yrs. after the first dose; Control group received first dose of Boostrix
- Planned to enroll 1467subjects (1100 from primary study and 337 Control)

*Brandon D et al. Antibody persistence and safety and immunogenicity of a second booster dose nine years after a first booster vaccination with a reduced antigen diphtheria-tetanus-acellular pertussis vaccine (Tdap) in adults. Vaccine (2018).

Boostrix 009 – Immunogenicity co-primary objectives

- Demonstrate Diphtheria (D) and Tetanus(T) seroprotection rates after second dose of Tdap, non-inferior to seroprotection rate after first Tdap dose.
  - One month after vaccination, lower limit (LL) of 97.5% confidence interval (CI) for difference between groups (second dose of Tdap [Boostrix/Adacel Groups] minus first dose of Tdap [Control Group]) is ≥ -10%
- Demonstrate PT, FHA, and PRN GMCs after second Tdap dose, non-inferior to infant immune response in the German household contact efficacy study.
  - One month after vaccination, LL of 97.5% CIs for pertussis antigen GMC ratios (Boostrix/Adacel Groups divided by Infanrix Group in German Household Efficacy Study) are ≥ 0.67
- Demonstrate D, T, PT, FHA and PRN Booster responses after second Tdap dose, non-inferior to immune response, after first Tdap dose.
  - One month after vaccination, LL of 97.5% CIs for difference between Groups (second dose of Tdap [Boostrix Group] minus first dose of Tdap [Control Group]) is ≥ -10% .
- Evaluate persistence of D and T antibodies at 1, 3, 5 and 9 years post initial vaccination.

Boostrix 009 – Secondary objectives

- Evaluate percentage of subjects with PT, FHA and PRN GMCs ≥ the assay cut-off, at 1, 3, 5 and 9 years post initial Tdap vaccination
- Evaluate D, T, PT, FHA and PRN GMCs at 1, 3, 5 and 9 years after initial vaccination with *Boostrix* and *Adacel*.
- Assess percentage of subjects with PT, FHA, and PRN GMCs ≥assay cutoffs, one month after re-vaccination.
- Assess immunogenicity of Boostrix in terms of D, T, PT, FHA and PRN GMCs, one month after vaccination.
- Explore the potential difference of D, T, PT, FHA and PRN GMCs between a second Tdap dose and a first Tdap dose
- Explore the potential difference in alternate booster responses for D, T, PT, FHA and PRN
- Safety of second and first Tdap doses - solicited local and general symptoms, unsolicited symptoms and SAEs

Boostrix 009 – Study population

	Tdap-B	Tdap-A	Control
Group definition	**Y0 Dose Boostrix Y9 Revaccination with Boostrix**	**Y0 Dose Adacel Y9 Revaccination with Boostrix**	**First Dose Boostrix**
Planned	733	367	367
Completed study at Year 9 (visit 6) without re-vaccination	166	94	-
Completed study at Year 9 (visit 7) after re-vaccination	306	136	357
ATP cohort for immunogenicity	271	121	327
Females: Males*	182:89	84:37	179:148
Mean age at Year 9 vaccination, years (SD)*	53 (28,73)	51.4 (28,73)	55 (28, 73)

*ATP cohort for immunogenicity

Boostrix 009 – Diphtheria & Tetanus seroprotection rates for re-vaccination with Boostrix were *non-inferior* to vaccination with a first dose of Boostrix

	Tdap-B group			Tdap-A group			Control group			Difference in Seroprotection Rates*					
										Tdap-B minus control*			Tdap-A minus control*		
	N	n	% ≥ 0.1 IU/mL	N	n	% ≥ 0.1 IU/mL	N	n	% ≥ 0.1 IU/mL		97.5% CI			97.5% CI	
											LL	UL		LL	UL
Diphtheria	271	269	**99.3**	121	120	**99.2**	326	319	**97.9**	**1.41**	**-1.16**	4.17	**1.32**	**-3.41**	4.15
Tetanus	271	271	**100**	121	121	**100**	327	326	**99.7**	**0.31**	**-1.52**	2.07	**0.31**	**-3.69**	2.07

*Bolded and shaded blue numbers indicate that the non-inferiority criterion has been met (the lower limit of the 97.5% CL ≥-10 for the difference in seroprotection rate)
N, number of participants with available results in each group
n (%), number/percentage of seroprotected participants (antibody concentration ≥0.1 international units [IU]/mL for diphtheria and tetanus)
CI, standardized asymptotic confidence interval
GMC, geometric mean concentration

Boostrix 009 – PT, FHA, and PRN re-vaccination GMCs are non-inferior to Infanrix GMCs in infant household efficacy study* (TVC)

	Comparator group*		Tdap-B group		Tdap-A group		GMC ratio					
	N	GMC	N	GMC	N	GMC	Tdap-B/Comparator			Tdap-A/Comparator		
								97.5% CI**			97.5% CI**	
								LL	UL		LL	UL
PT	2884	**41.7**	294	**64**	130	**68.6**	**1.53**	**1.31**	1.79	**1.64**	**1.33**	2.03
FHA	685	**47.2**	298	**248.8**	131	**248.8**	**5.27**	**4.62**	6.01	**5.27**	**4.37**	6.36
PRN	631	**113**	298	**408.7**	131	**504.8**	**3.62**	**3.07**	4.25	**4.47**	**3.58**	5.57

Bolded & shaded blue values indicate that the non-inferiority criterion has been met (the lower limit of the 95% CI for the GMC ratio ≥0.67)
* Infants vaccinated with Infanrix in a German Household efficacy study. Given the absence of serologic correlates of protection against pertussis, an immuno-bridging approach was used to assess immune responses to pertussis antigens, by extrapolating to the efficacy of a vaccine against pertussis as demonstrated in infants to an older age group.
**The associated CI for between-group GMC ratios were derived using Zou-Donner method
N, number of participants with available results in each group
CI, standardized asymptotic confidence interval
GMC, geometric mean concentration

Boostrix 009 – Booster response criteria for antigens

Antigen	Pre-vaccination Antibody Level	Booster Response Criteria
Diphtheria & Tetanus	<0.1 IU/mL	≥0.4 IU/mL
	≥0.1 IU/mL	≥4-fold increase
PT, FHA, PRN Assay thresholds (IU/mL): PT- 2.693 , FHA- 2.046 , PRN- 2.187	< assay cutoff	≥4 times assay cut-off
	between assay cut-off and <4 times assay cut-off	
	≥ 4 times assay cut-off.	≥2-fold increase compared to pre-booster levels

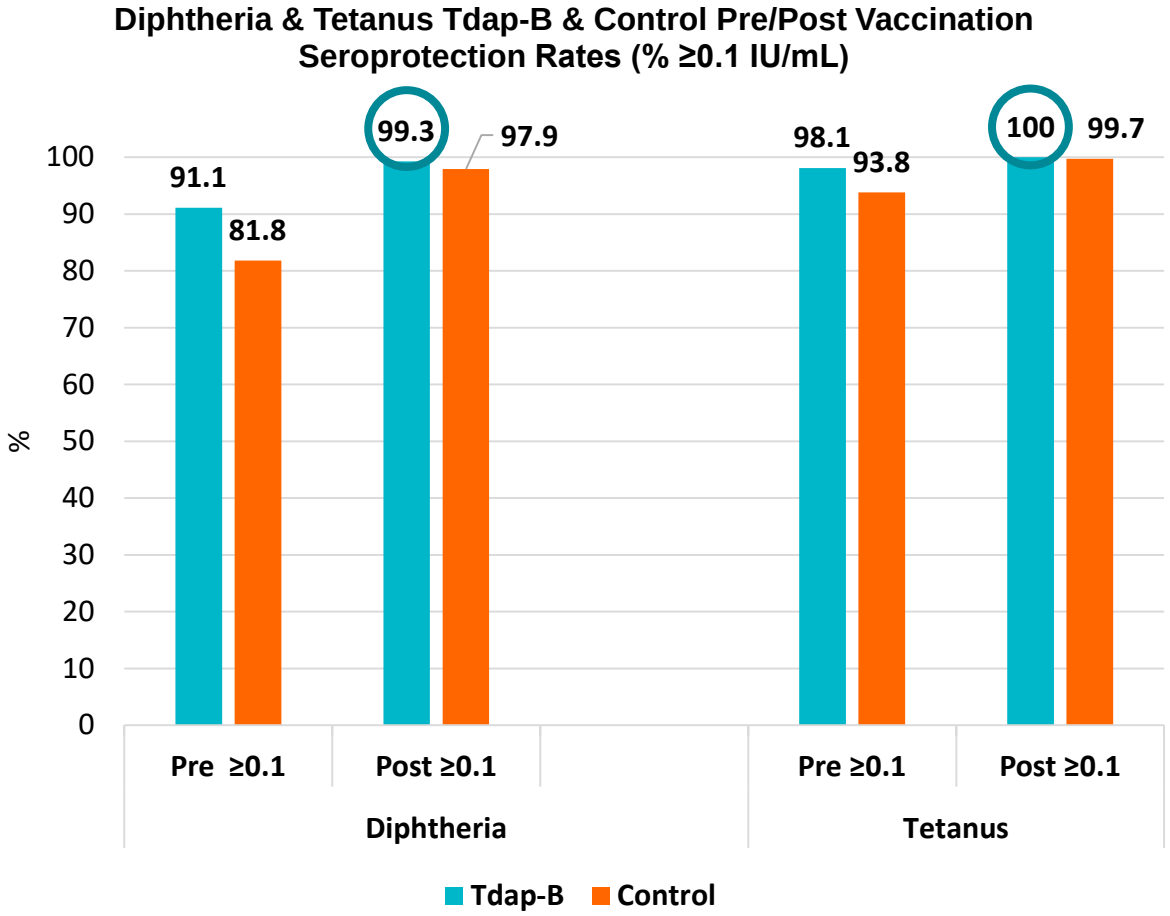
Boostrix 009 – Booster response rates* (immunogenicity ATP)

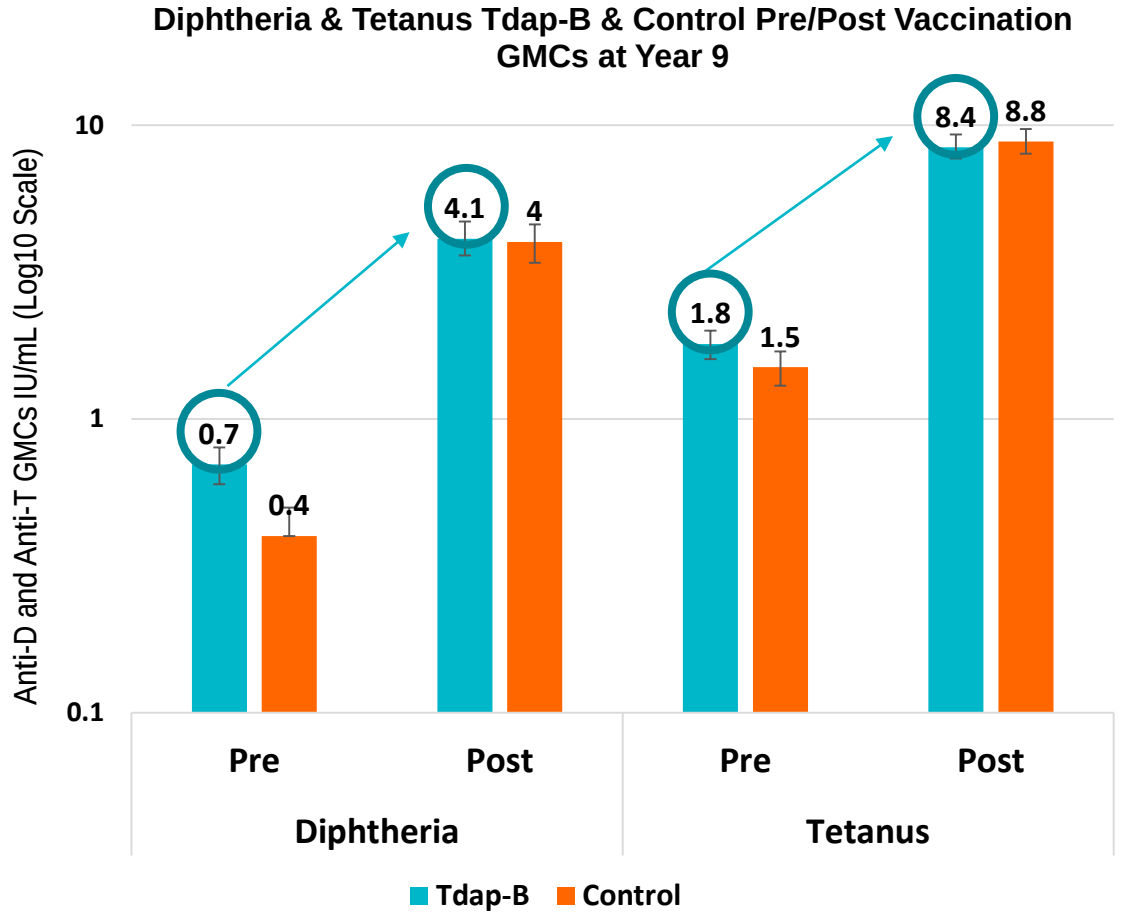
Non-Inferiority criteria met for PT in Tdap-B and FHA in Tdap-A groups

	Tdap-B group			Tdap-A group			Control Group			Difference in Booster Response Rates					
	N	n	%	N	n	%	N	n	%	Tdap-B minus control			Tdap-A minus control		
											97.5% CI			97.5% CI	
											LL	UL		LL	UL
Diphtheria	269	169	**62.8**	118	71	**60.2**	323	222	**68.7**	**-5.91**	**-14.67**	2.85	**-8.56**	**-20.33**	2.73
Tetanus	268	126	**47**	120	44	**36.7**	324	157	**48.5**	**-1.44**	**-10.63**	7.79	**-11.79**	**-22.98**	0.15
PT	271	235	**86.7**	120	106	**88.3**	326	292	**89.6**	**-2.85**	**-9.09**	3.08	**-1.24**	**-10.03**	5.57
FHA	271	232	**85.6**	120	116	**96.7**	327	303	**92.7**	**-7.05**	**-13.16**	-1.4	**4.01**	**-2.38**	8.66
PRN	271	210	**77.5**	118	98	**83.1**	320	281	**87.8**	**-10.31**	**-17.5**	-3.38	**-4.76**	**-14.53**	3.18

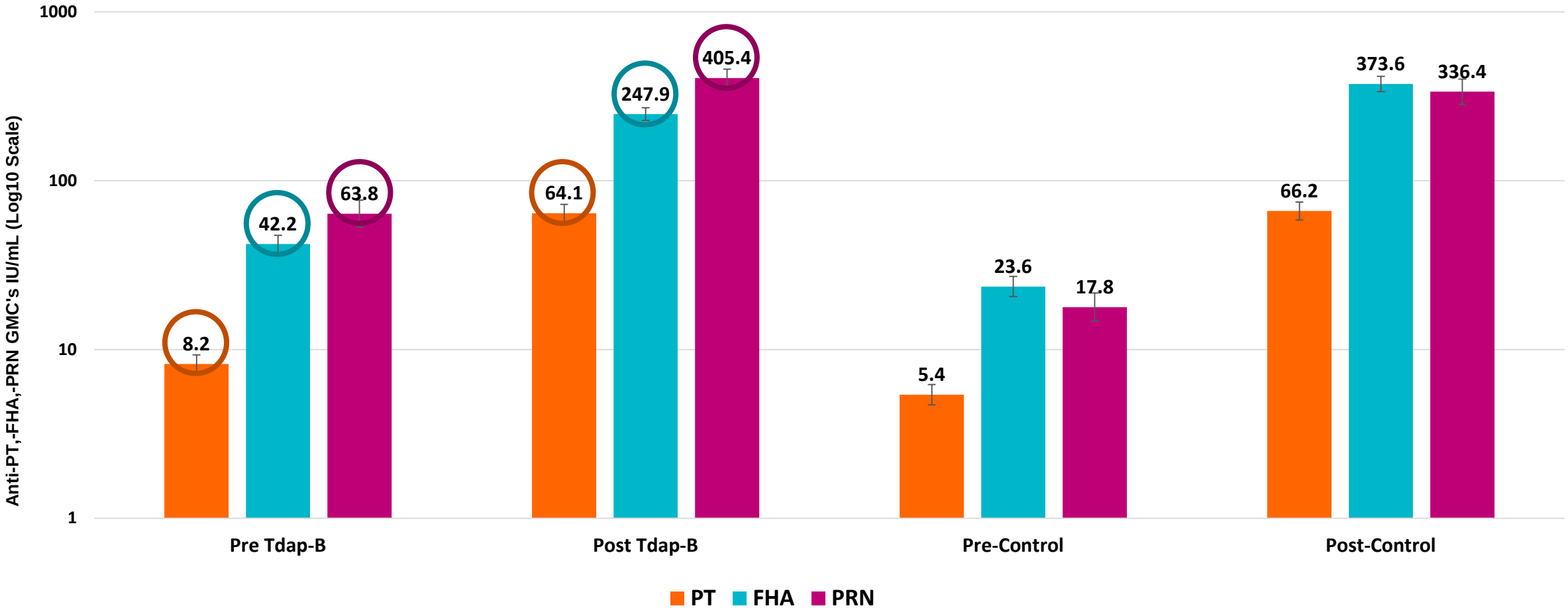
Bolded & shaded blue values indicate that the noninferiority criterion has been met. (the lower limit of the 97.5% CI for the difference in Booster Response Rates ≥ -10).
N, number of participants with available results in each group; n (%), number/percentage of seroprotected participants (antibody concentration ≥0.1 international units [IU]/mL for diphtheria and tetanus) or booster response; CI, standardized asymptotic confidence interval; GMC, geometric mean concentration

Boostrix 009 – Diphtheria & Tetanus *Tdap-B & control* pre/post re-vaccination seroprotection rates and GMCs at year 9

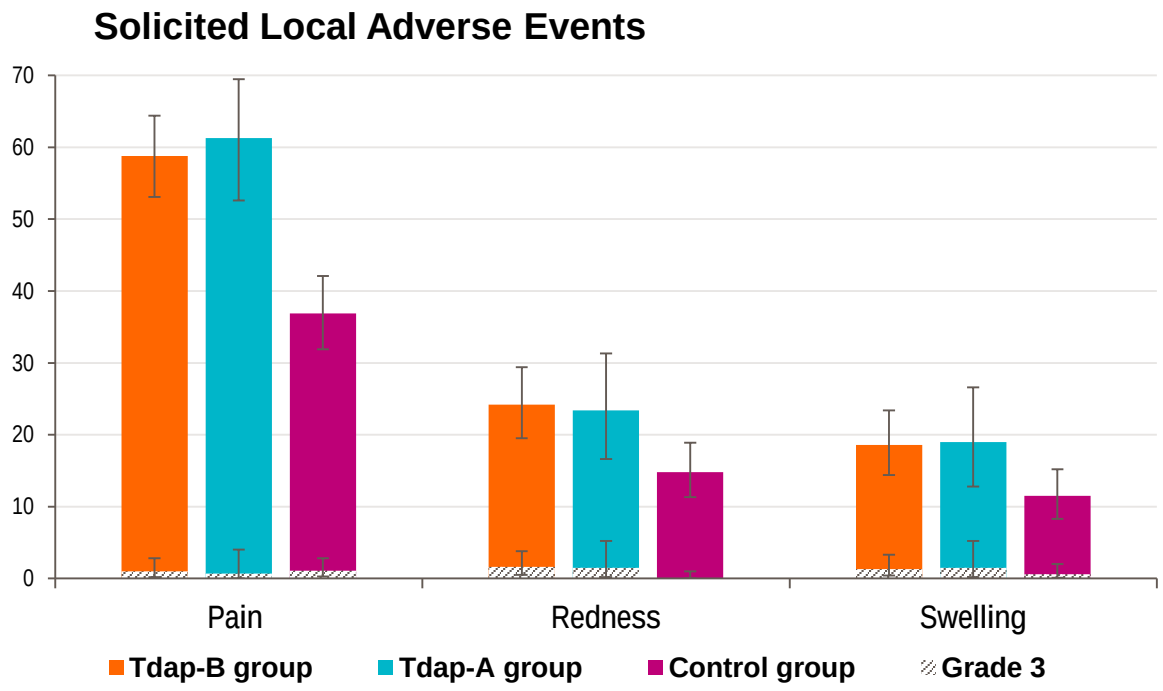


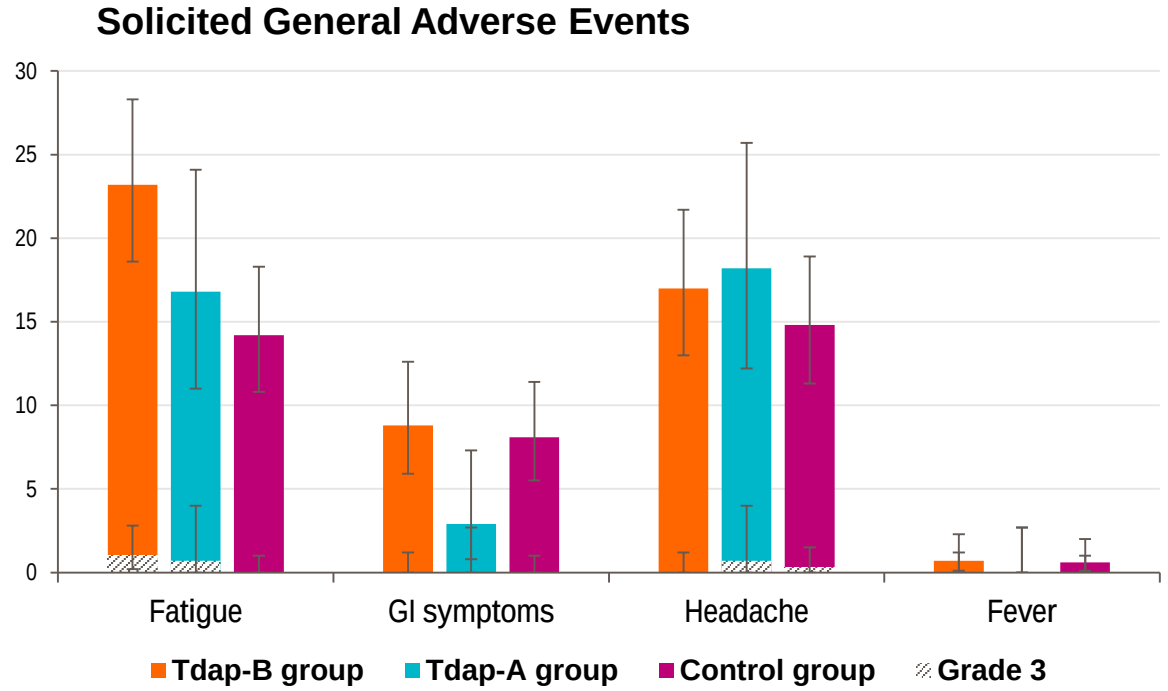


Boostrix 009 – PT, FHA, PRN *Tdap-B & control groups* pre/post re-vaccination *GMCs* at year 9



Boostrix 009 - solicited local & general adverse events vaccination at year 9



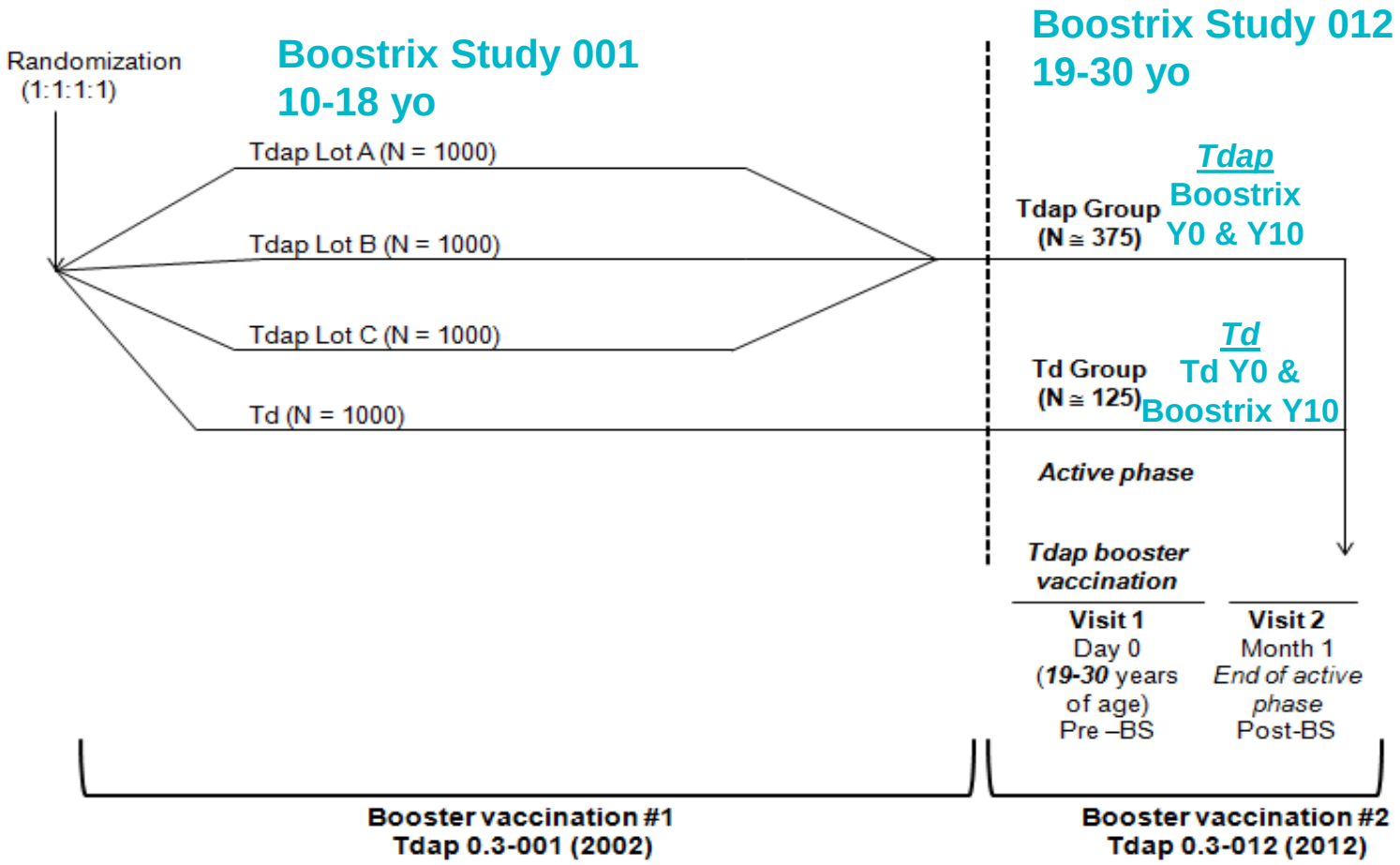


Unsolicited AEs: Vaccination related- 4.5% Tdap-B, 2.2% Tdap-A, 1.1% Control; Grade 3- 1.6% Tdap-B, 2.2% Tdap-A, 2,5% Control;
Most common unsolicited AE- Injection site bruising 1% Tdap- B & 0.7% Tdap-A; Injection site pruritis 1.3% Tdap-B.

Total vaccinated cohort; **GI**, gastrointestinal symptoms; **Fever**, temperature ≥37.5°C (99.5°F); **Grade 3**, diameter ≥50 mm (redness, swelling), preventing normal activity (pain, headache, fatigue, GI), temperature >40.0°C (104.0°F);.
Number of participants with the documented dose: Tdap-B: 306; Tdap-A:137; Control: 358.
Adapted from Brandon D et al. Antibody persistence and safety and immunogenicity of a second booster dose nine years after a first booster vaccination with a reduced Tdap in adults. Vaccine (2018),

Boostrix Study 012

Boostrix 012* – Study design



- A phase III, open-label, non-randomized, US multi-center, single-country study with two parallel groups
- Subjects who received Boostrix 10 years ago in study Tdap 0.3-001 were revaccinated with Boostrix and subjects who received Td received the first dose of Boostrix
- Planned to enroll 500 subjects

*Kovac M. et al. Immunogenicity and safety of a second booster dose of an acellular pertussis vaccine combined with reduced antigen content diphtheria-tetanus toxoids 10 years after a first booster in adolescence: An open, phase III, non-randomized, multi-center study. Human Vaccines & Immunotherapeutics. 2018

Boostrix 012 – Study population TVC

500 (planned) vs. 165 (enrolled)
Sensitivity analysis of persistence → no apparent bias related to dropout.

Number of subjects	Td group	Tdap group	Total
Group Definition	**Td at Y0 Boostrix at Y10**	**Boostrix at Y0 Boostrix re-vaccination at Y10**	
Planned, N	125	375	500
Enrolled , N (TVC)	37	128	165
Completed, n (%)	36 (97.3)	124 (96.9)	160 (97.0)
Females: Males	18:19	57:71	75:90
Mean Age, years (SD)	23.3 (2.4)	23.5 (2.1)	23.5 (2.1)
Median Age, years(min., max)	23 (20, 29)	23 (20, 29)	23 (20, 29)

N = total number of subjects
n/% = number/percentage of subjects
SD = standard deviation

Boostrix 012 – Co-primary objectives

- Demonstrate D and T seroprotection rates after a second Boostrix dose non-inferior to a first Boostrix dose
  - One month after vaccination, lower limit (LL) of 95% confidence interval (CI) for difference between groups (second dose of Tdap minus first dose of Tdap [Td- Control Group]) is ≥ -10%
- Demonstrate PT, FHA and PRN GMCs one month post revaccination, non-inferior to the infant GMCs in German household contact efficacy study
  - One month after vaccination, LL of 95% CIs for pertussis antigen GMC ratios (Boostrix Group divided by Infanrix Group German Household Efficacy Study) are ≥ 0.67

Boostrix 012 – Secondary objectives

- Assess persistence of D, T, PT, FHA, and PRN antibodies, 10 years after previous booster dose of Boostrix
- Assess immunogenicity of Boostrix in terms of PT, FHA and PRN GMCs> assay cutoffs, one month after vaccination.
- Explore potential difference in D, T, PT, FHA and PRN Booster response between second and first Boostrix dose
- Explore potential difference in D, T, PT, FHA and PRN GMCs between second and first Boostrix dose
- Safety of second and first Boostrix dose- solicited local and general symptoms, unsolicited symptoms and SAEs

Boostrix 012 – Diphtheria & Tetanus seroprotection rates for re-vaccination with Boostrix (Tdap) were non-inferior to vaccination with a first dose of Boostrix (Td control)

	Td group			Tdap group			Differences in Seroprotection Rates*		
	N	n	%	N	n	%	Tdap minus Td, %		
								95% CI	
								LL*	UL
Diphtheria	35	35	**100**	115	115	**100**	**0**	**-3.25**	9.95
Tetanus	35	35	**100**	115	115	**100**	**0**	**-3.25**	9.95

*Bolded and shaded blue numbers indicate that the non-inferiority criterion has been met (the lower limit of the 95% for the difference in seroprotection rate CI ≥-10)
Td group, participants receiving Td as first booster dose in the primary study and Boostrix as decennial booster dose (second booster dose) in the current study;
Tdap group, participants receiving Boostrix booster doses 10 years apart;
N, number of participants with available results;
n (%), number (percentage) of seroprotected participants (with anti-diphteria/tetanus antibody concentrations 0.1 IU/ml);
95% CI, 95% standardized asymptotic confidence interval; GMC, geometric mean antibody concentrations

Boostrix 012 – PT, FHA PRN revaccination GMCs were non-inferior* to GMCs in infant household efficacy study† (TVC)

	Comparator group*		Tdap group		Tdap/Comparator		
	N	GMC	N	GMC	GMC Ratio		
						95% CI	
						LL*	UL
PT	2884	41.7	124	83.5	**2.00**	**1.69**	2.37
FHA	685	47.2	124	285.5	**6.05**	**5.14**	7.11
PRN	631	113	124	442.6	**3.92**	**3.22**	4.76

*Bolded and shaded blue values indicate that the non-inferiority criterion has been met (the lower limit of the 95% CI for GMC ratio ≥0.67)
†Infants vaccinated with DTaP in a German efficacy study. Given the absence of serologic correlates of protection against pertussis, an immuno-bridging approach was used to assess immune responses to pertussis antigens, by extrapolating the efficacy of a vaccine against pertussis as demonstrated in infants to an older age group.

Td group, participants receiving Td as first booster dose in the primary study and Boostrix as decennial booster dose (second booster dose) in the current study;
Tdap group, participants receiving Boostrix booster doses 10 years apart;
N, number of participants with available results;
95% CI, 95% standardized asymptotic confidence interval;
GMC, geometric mean antibody concentrations

Boostrix 012 –Booster response rates (ATP Cohort)

Non-Inferiority criteria not met

	Tdap			Td			Difference in booster response rate (Tdap group minus Td group)		
								95 % CI	
	N	n	%	N	n	%	%	LL*	UL
Diphtheria	115	47	**40.9**	35	14	**40.0**	**0.87**	**-17.89**	18.28
Tetanus	115	64	**55.7**	35	21	**60.0**	**-4.35**	**-21.78**	14.49
PT	**115**	**106**	**92.2**	**35**	**33**	**94.3**	**-2.11**	**-10.03**	**11.33**
FHA	**115**	**104**	**90.4**	**35**	**34**	**97.1**	**-6.71**	**-14.23**	**5.54**
PRN	**115**	**79**	**68.7**	**35**	**29**	**82.9**	**-14.16**	**-27.43**	**3.21**

*Red Bolded values indicate that the noninferiority criterion has not been met. (non-inferior criteria were the lower limit of the 95% CI for the difference in Booster Response Rates ≥ -10).

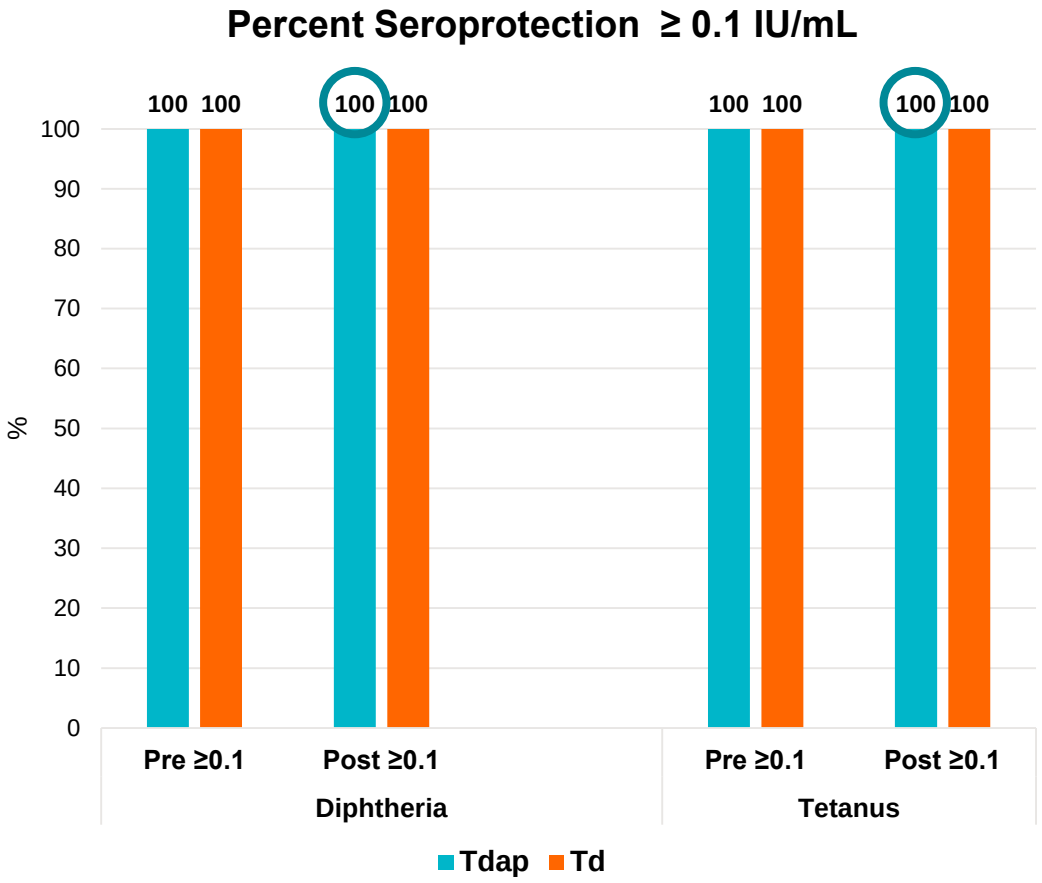
Td group = Subjects received the first dose of Boostrix Tdap vaccine

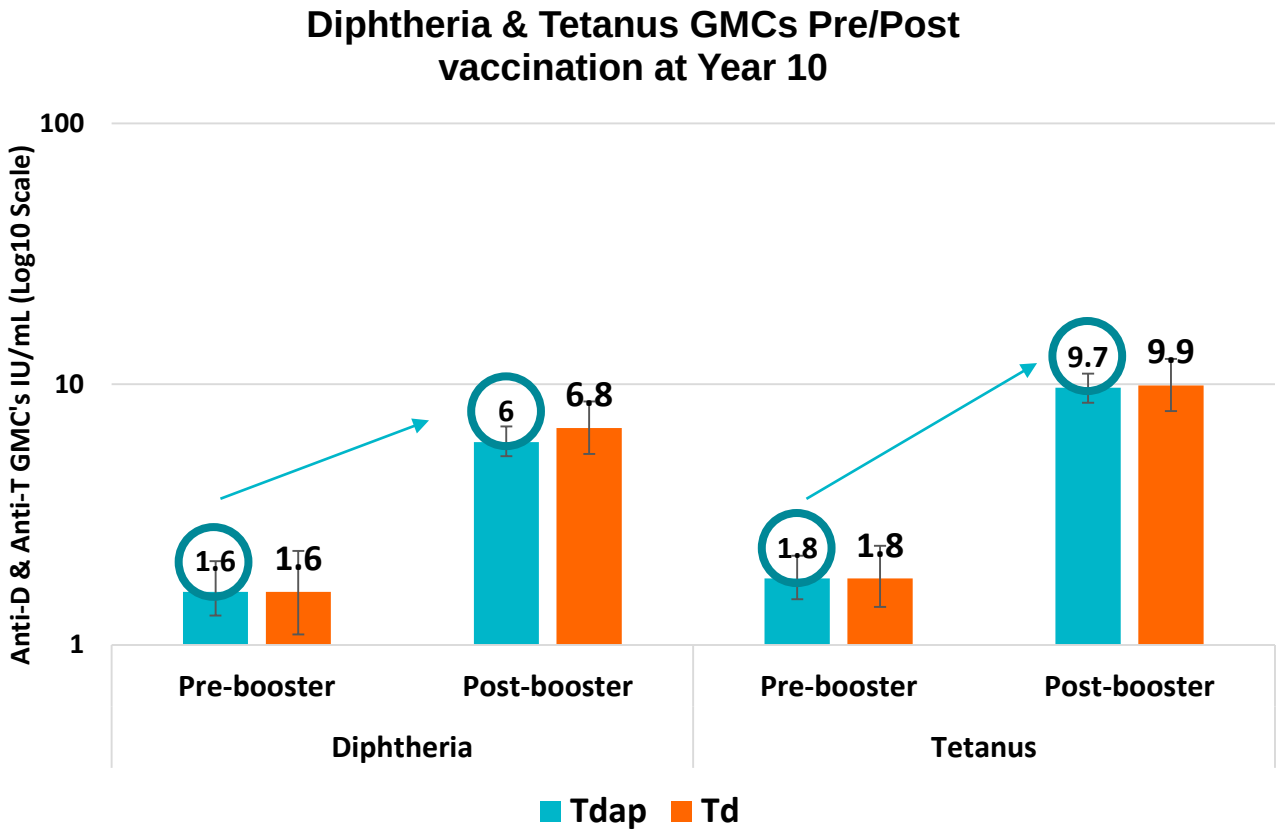
Tdap group = Subjects received a second dose of Boostrix vaccine

N = number of subjects with pre- and post-vaccination results available n/% = number/percentage of subjects with a booster response

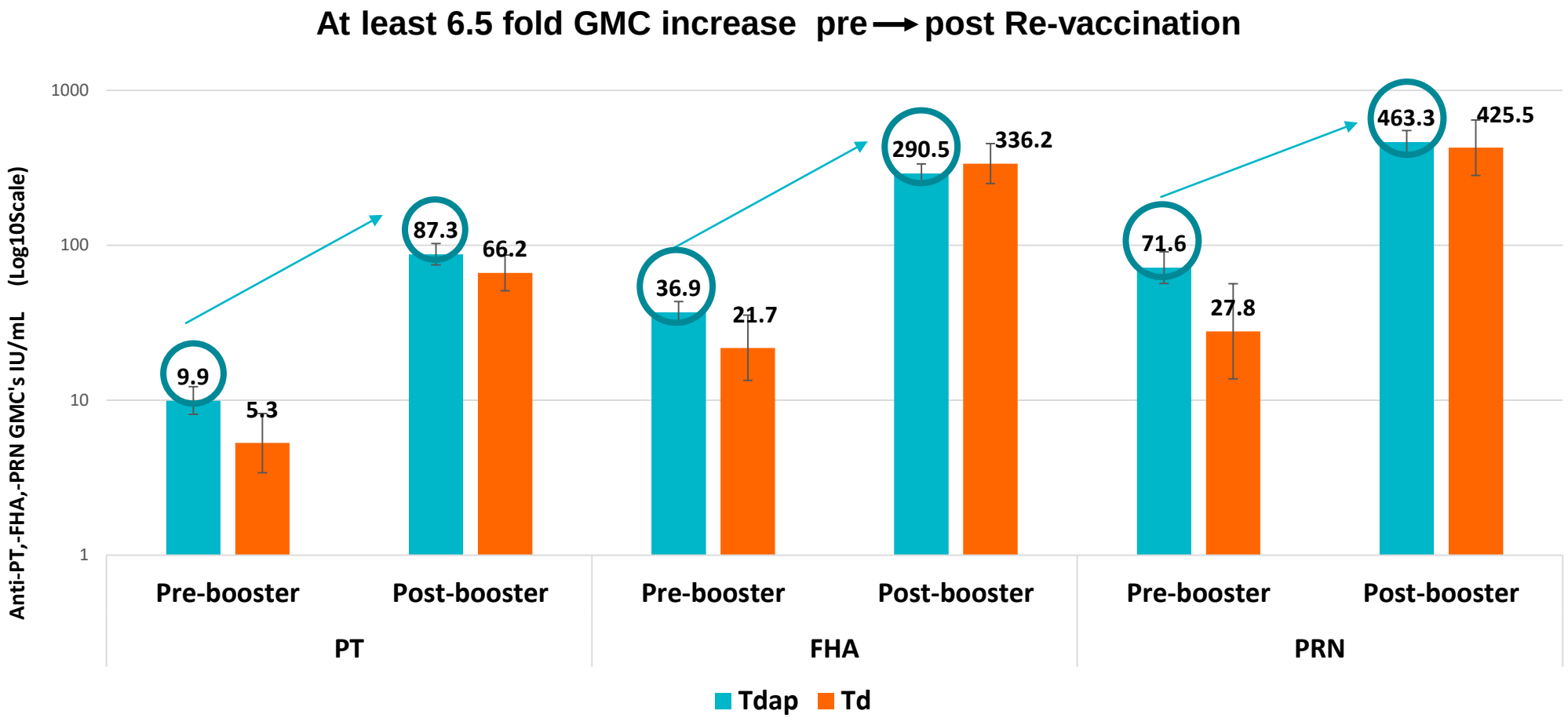
95% CI = Standardized asymptotic 95% confidence interval

Boostrix 012 – Diphtheria & Tetanus pre/post re-vaccination seroprotection rates & GMCs at year 10

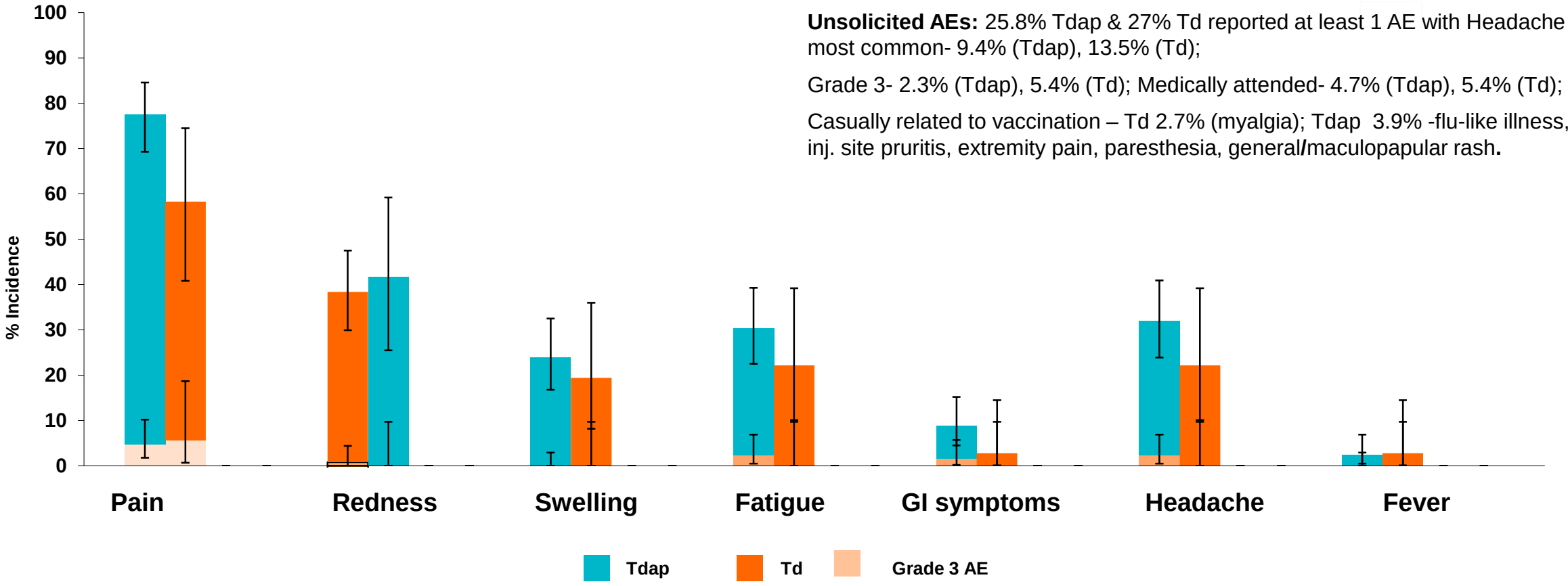




Boostrix 012 – PT, FHA & PRN GMCs, Pre-/Post- Re-vaccination at Year 10



Boostrix 012 – Percent of Subjects with Solicited Local and General Adverse Events



Unsolicited AEs: 25.8% Tdap & 27% Td reported at least 1 AE with Headache most common- 9.4% (Tdap), 13.5% (Td);

Grade 3- 2.3% (Tdap), 5.4% (Td); Medically attended- 4.7% (Tdap), 5.4% (Td);

Casually related to vaccination – Td 2.7% (myalgia); Tdap 3.9% -flu-like illness, inj. site pruritis, extremity pain, paresthesia, general/maculopapular rash.

Boostrix 009 & Boostrix 012 – Summary

- Boostrix Study 009 and 012 were revaccination studies with Boostrix at 9 and 10 years, respectively
- Both studies met noninferiority endpoints:
  - Seroprotection rate (% subjects ≥0.1 IU/mL) for Diphtheria, Tetanus (primary endpoint)
  - GMC ratio* for PT, PRN and FHA (primary endpoint)
- Both studies groups' that received revaccination with Boostrix missed booster response endpoints** ; however:
  - Seroprotection rates for Diphtheria & Tetanus of ≥0.1 IU/mL and ≥1.0 IU/mL, respectively, were achieved by
    - > 99% and >91%, of subjects in both studies
  - Pertussis antigen GMC fold rise pre to post re-vaccination were at least 6 fold in both studies †
- Solicited symptoms (local and general) were generally higher after dose 2 than dose 1, Grade 3 symptoms similar after dose 1 and dose 2

*Revaccination GMC *divided by* GMC from Infant Household Efficacy study
**Booster response was co-primary endpoint in study 009 and secondary endpoint in study 012
† Pertussis GMC fold rises for Boostrix Study 009 (groups Tdap-B, Tdap-A) and Study 012 (Tdap), respectively were : PT 7.8, 9.0, 8.8; FHA 5.9, 8.9, 7.9; PRN 6.4, 7.9, 6.5

Conclusion – Boostrix is immunogenic and well-tolerated

Boostrix when administered to adults 19-73 years of age, 9-10 years after previous vaccination, is immunogenic and well tolerated.

Thank You