

GRADE TABLE 1a**Population:** Children and adolescents.**Intervention:** 6 Tetanus Toxoid Containing Vaccine (TTCV) doses including a 3-dose primary series and 3 booster doses during childhood and adolescence.**Comparison:** No vaccination or using less than 6 TTCV doses during childhood.**Outcome:** Tetanus cases.

PICO Question: <i>Will a complete 6-dose schedule of TTCV during childhood provide protection throughout the reproductive age or longer as compared to no vaccination or using less than 6 doses during childhood?</i>				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		3 Observational ¹	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	Serious ²	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of certainty of evidence			1
Summary of Findings	Statement on certainty of evidence			Evidence supports a very low level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			Six doses of TTCV by adolescence are expected to protect for at least 20-30 years and throughout the reproductive age. Even though the seroprevalence data are indirect, they suggest that children that who received 6 doses will have persistent levels of protective tetanus-specific antibody. ³

¹ From a systematic review of literature, 1 observational study was identified [1] that demonstrated that at approximately 20 years after the last dose the geometric mean titre was 0.44 IU/ml. The completion of a 6-dose TTCV schedule of 3 primary doses and 3 booster doses is expected to provide protective antibody levels ≥ 0.01 IU/ml for 20-30 years. From a regression analysis, de Melker et al. predict that the geometric mean titre would be 0.22 IU/ml at 90 years of age approximately 80 years after the sixth TTCV dose. Steens et al [2] in 2010 confirmed adequate TT-antibody concentration throughout most of reproductive rates with even higher tetanus-antitoxin antibody geometric mean concentration (IU/ml) throughout all age-groups ten years after the first study. Another comparative study was identified [3] that concluded that 6 doses of TTCV confers protection for at least 20 years. All participants that began vaccination during childhood with DPT and had been vaccinated in that last 20 years, had a geometric mean antibody level ≥ 0.01 IU/ml.

² Protective antibody levels ≥ 0.01 IU/ml were used as a proxy to indirectly measure tetanus cases. Even though the antibody level was significantly greater than the protective antibody level, it remains uncertain if this will also translate in a lower protection against clinical disease. Further, small sample size of one study was small. [3].

³ Other supporting evidence for the duration of protection of 6 TTCV includes that [4] tetanus-specific antibodies have a half-life of 11 years, [5] tetanus-specific antibody concentrations > 1.0 IU/ml are predicted to confer at least 20 years of protection and [6] mathematical modeling suggests that 95% of the population will remain seroprotected against tetanus for up to 72 years without further booster vaccination after childhood vaccination (based on a 14-year half-life and a protective threshold of 0.01 IU/ml). Hammarlund et al. predict that individuals would remain protected without addition booster doses for at least 30 years.

References

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- [3] Gonçalves G, Santos MA, Frade JG, Cunha JS. Levels of diphtheria and tetanus specific IgG of Portuguese adult women, before and after vaccination with adult type Td. Duration of immunity following vaccination. *BMC Public Health*. 2007;7:109.
- [4] Amanna IJ, Carlson NE, Slifka MK. Duration of Humoral Immunity to Common Viral and Vaccine Antigens. *New England Journal of Medicine*. 2007 Nov 8;357(19):1903–15.
- [5] Ölander R-M, Auranen K, Härkänen T, Leino T. High tetanus and diphtheria antitoxin concentrations in Finnish adults—Time for new booster recommendations? *Vaccine*. 2009 Aug 27;27(39):5295–8.
- [6] Hammarlund E, Thomas A, Poore EA, Amanna IJ, Rynko AE, Mori M, et al. Durability of Vaccine-Induced Immunity Against Tetanus and Diphtheria Toxins: A Cross-sectional Analysis. *Clin Infect Dis*. 2016 May 1;62(9):1111–8.