

WHO/UNICEF GUIDANCE NOTE

Ensuring Sustained Protection Against Diphtheria: Replacing TT with Td vaccine

Since 1998, WHO has recommended that tetanus toxoid (TT) should be replaced by tetanus-diphtheria (Td) vaccine. This is reiterated in the WHO tetanus vaccine position paper of 2017¹ which highlights slow-uptake of the recommended replacement. The rationale for replacing TT with Td vaccine is the need to sustain protection against diphtheria due to waning diphtheria immunity following the primary series of DTP-containing vaccine given in the first year of life. There is a scientific consensus that from the age of 4 years Td vaccine² can be used instead of TT, including during pregnancy. By replacing TT with Td, additional protection against diphtheria can be obtained without major changes to the immunization programme and schedule. However, the awareness and adoption of this recommendation at country level remains low.

This document provides guidance to Ministries of Health and to national and senior level programme managers in those countries yet to replace TT with Td vaccine in their national immunization programmes. Information is provided on the major considerations and steps required for a smooth and successful transition from the use of TT to Td vaccine.

In light of the important public health benefits of replacing TT with Td, as of 1 January 2020 UNICEF will no longer supply TT vaccine.³

Background: the threat of diphtheria

Tragically in 2018, with outbreaks in Bangladesh, Haiti, Kenya, Indonesia, Venezuela and Yemen, diphtheria is headline news. Why? Because not all children are receiving three doses of diphtheria-containing vaccine during infancy, but also because many programmes do not provide booster vaccination of older age groups against diphtheria that is vital to combatting waning immunity.

Serious diphtheria epidemics in Eastern Europe and South America in the early and mid-1990's revealed that immunity to diphtheria wanes following the primary series of DTP infant immunization. It was also found that the immune boosting effect from natural infection is lost in areas with long-term

Diphtheria Disease

Diphtheria is a potentially fatal disease in at least 10 percent of cases that occur, and if left untreated, can cause severe damage to the kidneys, nervous system, and heart. Even if there are no signs or symptoms, an infected person is able to transmit the infection for up to four weeks.

¹ WHO Tetanus Vaccine: Position Paper February 2017. Weekly Epidemiological Record, 10 Feb. 2017, Vol 92, 6 (pp. 53-76)
http://www.who.int/immunization/policy/position_papers/tetanus/en/

² Tetanus-diphtheria (Td, low-dose diphtheria toxoid) formulations can be used from 4 years of age, and must be used for all those > 7 years of age. This reduction of diphtheria toxoid potency minimizes reactogenicity at the injection site but is still sufficient to provoke an antibody response in older children and adults. The higher potency of diphtheria vaccine (D) is used for primary vaccination of young infants (DTP-containing vaccines).

³ However, an exception will be made for TT vaccine in compact cPAD devices such as UNIJECT, as Td products in this presentation are not yet available.

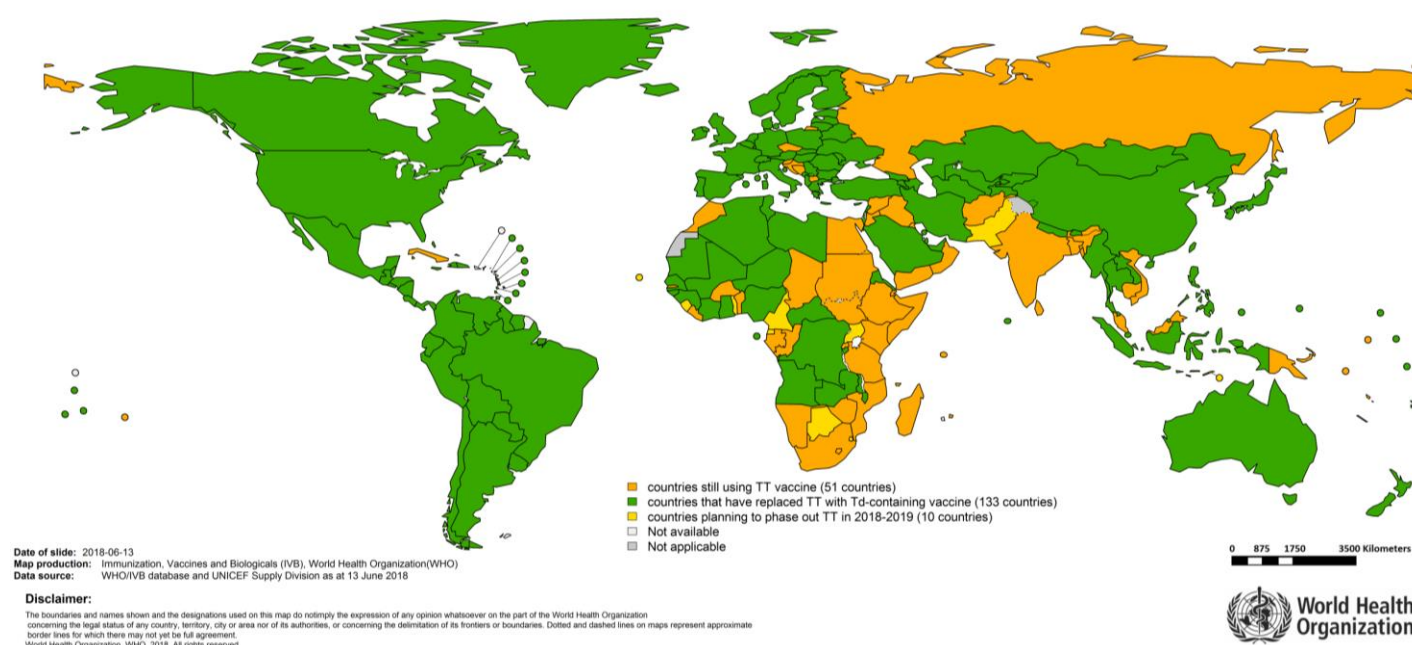
high DTP3 coverage. The result was a resurgence of outbreaks in countries previously thought to have been fully protected through immunization.

After experiencing outbreaks, these regions changed to tetanus and diphtheria-containing (Td) vaccine for women of reproductive age, and provided Td booster doses for older children and adolescents. This strategy, along with achieving high coverage, resulted in diphtheria very nearly disappearing in Eastern Europe and South America.

To avoid the threat of diphtheria outbreaks, since 1998 WHO has recommended that all countries replace TT with Td for vaccination of women of reproductive age (and/or pregnant women as per national immunization target), older children and adolescents to improve protection against diphtheria. The WHO position paper on diphtheria vaccine provides the background for this recommendation.⁴

Td has been proven to be safe and cost effective. Globally, however, the replacement of TT with Td vaccine has been incomplete and slow. Available WHO and UNICEF joint reporting form (JRF) and UNICEF Supply Division data as at end of May 2018 show that only 133 countries are fully using Td instead of TT vaccine and 61 countries are still using TT vaccine in their national immunization programme (Figure 1). Ten of these already planning for the replacement between 2018 and 2019⁵; nothing is yet planned for the remaining 51 countries.⁶

Figure 1. Status of countries' replacement of TT with Td in their routine immunization programme



⁴ WHO Position Paper August 2017 – Diphtheria Vaccine http://www.who.int/immunization/policy/position_papers/diphtheria/en/

⁵ 10 countries already planning for the TT to Td replacement in 2018/2019: Botswana, Cameroon, Cabo Verde, Equatorial Guinea, Pakistan, Sierra Leone, Swaziland, Timor-Leste, Togo and Uganda.

⁶ 51 countries not yet planning for the TT to Td replacement: Afghanistan, Bangladesh, Benin, Bosnia and Herzegovina, Burkina Faso, Cambodia, Chad, Comoros, Congo, Cook Islands, Croatia, Cuba, Czech Republic, Djibouti, Egypt, Ethiopia, Gabon, Gambia, India, Iraq, Jordan, Kenya, Kuwait, Lesotho, Liberia, Madagascar, Malaysia, Mauritius, Morocco, Mozambique, Namibia, Nauru, Oman, Papua New Guinea, Russian Federation, Rwanda, Seychelles, Slovenia, Solomon Islands, Somalia, South Africa, South Sudan, Sri Lanka, Sudan, Syrian Arab Republic, The former Yugoslav Republic of Macedonia, United Republic of Tanzania, Vanuatu, Viet Nam, Yemen and Zimbabwe.

Why make the change from TT to Td?

❖ Waning immunity and low circulation of natural infection resulting in resurgence of diphtheria disease

In the absence of natural boosting, data indicate that diphtheria immunity following a 3-dose primary vaccination schedule wanes over time.⁷ Therefore, booster doses of diphtheria toxoid containing vaccines are needed to ensure continuing protection. WHO recommends a schedule of 3 primary doses plus 3 booster doses for diphtheria vaccination.²

❖ Weak early detection and disease surveillance systems

Unfortunately, surveillance systems are not sensitive to the early detection of diphtheria in areas where the disease appears to have 'disappeared'. Diphtheria incidence data are underreported by countries, particularly in the African and Eastern Mediterranean regions.⁷ This lack of data may explain why the replacement of TT with Td is a low public health priority in some countries. Epidemiological surveillance should be strengthened to ensure early detection and medical management of diphtheria outbreaks, as well as, access to laboratory facilities for reliable identification of toxigenic *C. diphtheriae*.

❖ Limited availability of a national protocol for the management of diphtheria and access to anti-toxin

Some countries do not have a national protocol to guide the optimal medical management of diphtheria cases. There is often inadequate access to diphtheria antitoxin (DaT), which is crucial to lessen the severity of disease. With the uncertainty of diphtheria outbreaks, it is easier and more cost saving to prevent disease through immunization than rely on management of cases and the financial and human resource burden of contact tracing and post-exposure prophylaxis.

❖ Value added of replacing TT with Td vaccine

Td vaccine offers protection against two diseases without any programmatic changes, including similar estimated vaccine wastage rates, and at very minimal additional cost, especially if the same vial sizes are used. Td can be used for the population from 4 years of age under all circumstances, such as school immunization programmes, antenatal care and supplementary vaccination campaigns. Moreover, the safety profiles of Td and TT vaccines are comparable. Both TT and Td vaccine are available in the global market in 1, 10 and 20 dose preparations.

The cost increase per dose for Td vaccine is marginal – an additional \$US 0.01 – 0.03 per dose via UNICEF (Table 1) -- yet it can make a significant reduction in disease incidence.

The tetanus-diphtheria (Td) vaccine market is a healthy market, with ample capacity and five suppliers with WHO pre-qualified Td vaccine, four of which are actively supplying and have in-house production of tetanus and diphtheria bulk, with an estimated capacity of approximately 300 million doses per annum. The global demand for tetanus toxoid containing vaccines is approximately 250 million doses, of which 160 million doses are supplied through UNICEF. Therefore, there is sufficient supply of Td vaccines for all countries to replace TT with Td in their immunization schedule.

⁷ See Immunological basis for immunization: Diphtheria (Update 2009) at http://apps.who.int/iris/bitstream/handle/10665/44094/9789241597869_eng.pdf and CDC, 2017. Review Of The Epidemiology Of Diphtheria – 2000-2016 http://www.who.int/immunization/sage/meetings/2017/april/1_Final_report_Clarke_april3.pdf

Table 1. Comparison of UNICEF prices for TT and Td vaccine

Vaccine (vial size)	Price \$USD / dose
TT (10 dose)	\$0.080 - 0.13
Td (10 dose)	\$0.10 - 0.13
TT (20 dose)	\$0.0531 - 0.085
Td (20 dose)	TBC (forthcoming by end 2018 after UNICEF completes its current tender process)

UNICEF Supply Division holds long-term agreements for Td vaccine with four manufacturers; Bio Farma (P.T. Persero), Intervax, Biological E and Serum Institute of India Ltd. UNICEF vaccine prices can be found under the following link: https://www.unicef.org/supply/files/2018_03_01_Td.pdf

Value Added Example: The marginal increased cost of Td vaccine

Country X has a total population of 1,000,000 (one million)

**Cost difference for replacing TT with Td estimated using a 10 dose vial at average price quoted from UNICEF Supply Division.*

- Pregnant women** (representing approximately 3-4% of a population), the target population would be 40,000.
 Calculated cost for TT vaccine = 40,000 x US\$ 0.08 = US\$ 3,200
 Calculated cost for Td vaccine = 40,000 x US\$ 0.10 = US\$ 4,000
 An additional cost of US\$ 800 for the protection against two diseases without any programmatic change.
- Women of reproductive age** (representing approximately 22% of a population), the target population would be 220,000.
 Calculated cost for TT vaccine = 220,000 x US\$ 0.08 = US\$ 17,600
 Calculated cost for Td vaccine = 220,000 x US\$ 0.10 = US\$ 22,000
 An additional cost of US\$ 2,400 for the protection against two diseases without any programmatic change.

There are also several (9) Td vaccine products non-prequalified and various other Td combination products (Tdap, Td-IPV and Tdap-IPV), for an additional capacity of about 80 million and potential to expand further. More information on supply and on pricing for self-procuring countries, including for non-prequalified products and combination products, can be found here: www.who.int/immunization/MI4A

The global demand for tetanus toxoid containing vaccines is approximately 250 million doses, of which 160 million doses are supplied through UNICEF. Therefore, there is sufficient supply of Td vaccines for all countries to replace TT with Td in their immunization schedule.

Table 2. Schedule for TT-containing vaccines

Target population	Recommended Tetanus & Diphtheria Vaccination Schedule			Total doses
Childhood	3 primary doses of TTCV (DTP-containing) Starting from 6 weeks of age, 3 doses should be provided before 1 year, with minimum 4 week intervals between doses	3 booster doses		
		12-23 months	4-7 years	9-15 years
		DT-containing (eg. DTwP or DTaP or penta or quadra)	Td can be used from ≥4 years (but must be used if ≥ 7 years)	Td
				6

				OR DT-containing (if < 7 years)		
Children >1 year with no previous immunization^{8,9}	DTP-containing as early as possible	DTP-containing at least 4 weeks after first dose	DTP-containing at least 6 months later	At least 1 year later DTP-containing/Td	At least 1 year later DTP-containing/Td	5
Adolescents and adults with NO previous immunization including pregnant women¹⁰	Td as early as possible	2 nd dose of Td at least 4 weeks after first dose	3 rd dose of Td at least 6 months later	Td booster at least 1 year later	Td booster at least one year later	5
Pregnant women who received 3 childhood DTP-containing doses	Td as early as possible in first pregnancy	2 nd Td dose at least 4 weeks after first dose and 2 weeks before birth	Td at least 1 year later or in next pregnancy			6
Pregnant women who received 4 childhood DTP-containing doses	Td as early as possible in first pregnancy	Td at least 1 year later or in next pregnancy				6
Supplementary immunization activities (SIA) in high-risk areas for women of child-bearing age	Td in round 1	Td in round 2 (4 weeks after round 1)	Td in round 3 at least 6 months after round 2	Td at least 1 year later or in next pregnancy	Td at least one year later or in subsequent pregnancy	5

Why has TT not yet been replaced with Td in SOME countries?

- Not yet a priority and lack of awareness:
 - WHO's recommendation that TT be replaced with Td has not been adequately communicated.
 - The National Technical Advisory Group (NITAG) has not yet reviewed the evidence and presented justification for the change to the Ministry of Health.
 - The Ministry of Health is not yet fully on board because Td replacement is not seen as an urgent matter when there are apparently no reported cases of diphtheria.
- Confusion with the schedule and strategies:
 - Some countries have booster doses of Td for older children and adolescents, but continue to use TT for adults, particularly pregnant women.
 - Some countries have a mixed schedule that uses both TT and Td for the same target populations but the type of vaccine used varies geographically.
 - Some countries use Td in their national immunization schedule, but use TT vaccine for campaigns for the elimination of maternal and neonatal tetanus or vice versa.
- Vaccine production and procurement:
 - Partners (UNICEF, WHO and others) who advise and assist countries with their immunization programmes have not actively discouraged procurement of TT. In the region of the Americas the change from TT to Td was largely driven by the decision of PAHO's Revolving Fund to phase out the availability of TT vaccine.
 - Local production of TT vaccine prevents changing to Td vaccine. There is little understanding that it is not cost effective to produce TT.
 - Countries that self-procure need to be convinced of the cost effectiveness of purchasing a vaccine which is only marginally more expensive but which provides protection against two diseases.

⁸ Other tetanus containing combination vaccines such as pentavalent vaccine should be used per the national immunization schedule.

⁹ If ≥ 7 years old use only aP containing vaccine; if ≥ 4 years old Td containing vaccine is preferred and should only be used for those ≥ 7 years of age.

¹⁰ For pregnant women, the second dose should be administered at least 2 weeks before giving birth. Doses 3-5 may also be provided during subsequent pregnancies.

Six Action Steps to make the change from TT to Td

1. **Organize a process for review and decision-making:** The Ministry of Health, through its NITAG or with partners, should organize a process to review the current situation and officially recommend the replacement of TT with Td. Bear in mind that diphtheria surveillance may be suboptimal in many countries and national evidence alone may not be adequate. Sustained protection against diphtheria requires adopting a life-course approach to vaccination, including the introduction of booster doses for children and adolescents, and for adults who were insufficiently vaccinated or did not receive booster doses.
2. **Plan, budget and forecast:** Determine the optimal time to implement the replacement of TT with Td vaccine and ensure that financial resources/budget lines are available to cover any marginal increased costs (both for vaccine and any additional vaccination visits of older age groups). Update the national comprehensive Multi-Year Plan (cMYP) for immunization to reflect the changes. Countries procuring through UNICEF should ensure that their requirement is included in the UNICEF Supply Division (SD) annual forecast, while indicating the preferred presentation of Td vaccine.
3. **Revise materials:** Revise and disseminate the national immunization schedule to include Td. Update national immunization technical guidance as needed and adjust home-based records and reporting forms/registers/etc. to accommodate use of Td vaccine. Ensure that the surveillance and protocol for monitoring adverse events is updated accordingly.
4. **Train health professionals:** Plan to educate health workers about changing from TT to Td and the need for booster vaccination through information flyers, refresher-training, and other channels. Remember to include private sector practitioners in these efforts.
5. **Inform and raise awareness:** Notify the population through social mobilization and community advocacy activities, about the benefits of replacing TT with Td vaccine and the importance of vaccination throughout the life-course.
6. **Procure Td vaccine:**
 - a) If procuring through UNICEF, contact local staff and submit a 5-year plan for procurement of Td.
 - b) If self-procuring, contact manufacturers to negotiate Td replacement for the next vaccine procurement.

Important:

As of January 2020, UNICEF will no longer fund TT vaccine, nor provide procurement services for supply of TT vaccine. UNICEF will continue to support Td vaccine only, in support of maternal immunization programmes.

FOR FURTHER INFORMATION

For further information see attached communique and Q & A and contact:

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