Adult Tetanus Toxoid and Tetanus-Diphtheria Vaccines Market & Supply Update

UNICEF Supply Division

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1. Summary

- UNICEF procures adult tetanus-containing vaccines, namely tetanus toxoid (TT) and tetanus-diphtheria (Td) combination vaccines, for use in routine immunization (RI) and campaigns primarily in support of maternal and neonatal tetanus elimination (MNT), and adult diphtheria prevention. For the purpose of this note, TT/Td excludes paediatric diphtheria tetanus (DT) and all paediatric pertussis-containing vaccines (DTP, DTP-HepB, DTP-Hib and Pentavalent vaccines: DTP-HepB-Hib).
- TT/Td vaccine supply availability through UNICEF is sufficient to meet forecasted country requirements. From 2005 to 2014, TT/Td vaccine supply availability was stable and averaged approximately 150 million doses a year covering the needs of 80-100 countries, of which 20% was for campaign activities. Over the period, TT vaccine procurement accounted for 95% of total TT/Td procurement through UNICEF.
- In 2006, The World Health Organization (WHO) recommended countries transition from TT to Td in order to strengthen and expand adult protection against diphtheria. Initially, many countries did not make the transition, and Td vaccine procurement through UNICEF averaged only 3% (4 million doses) of annual TT/Td volumes from 2005 through 2011. More recently, switching to Td has increased, reaching 12% (18 million doses) of total TT/Td volumes procured through UNICEF in 2014.
- UNICEF anticipates overall TT/Td forecasted demand to reach 165 million doses a year during 2016-2017, and anticipates an increasing share of Td vaccines. However, Td vaccine country demand forecasts remain somewhat uncertain and are dependent on country TT/Td transition decisions and timing.
- UNICEF launched its TT/Td vaccine tender in June 2015 to supply 165 million doses a year over 2016-2017 to meet country demand for RI and campaign activity. UNICEF awarded long-term arrangements (LTA) in October 2015 to five suppliers.

2. General Brief and Background

Tetanus is an acute bacterial infection caused by Clostridium Tetani. It can affect all age groups, but umbilical cord infection during delivery is the most common form, affecting newborn babies and mothers in resource-limited settings. Case mortality of tetanus can be 100%, if untreated, and can range between 10%-60% even under hospitalised care. There is no natural immunity against tetanus, although clean delivery practices can help prevent infection. WHO estimates global maternal and neonatal tetanus (MNT) mortality to have reduced by 76% from 2000, to reach 49,000 in 2014, although tetanus deaths, particularly among neonates, are often unreported. In addition to infant and childhood diphtheria, tetanus and pertussis (DTP) immunization, WHO recommends immunization with adult TT/Td primarily to address MNT. Longer-lasting immunity for at least five years can be engendered among pregnant women through additional immunization with two doses of TT/Td provided at least 4 weeks apart, and a 3rd dose provided 6 months after the second dose.

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1 World Health Organization, Tetanus Fact Sheet, WHO, Manila, February 2012.
UNICEF, together with WHO, the United Nations Population Fund (UNFPA) and partners, lead neonatal tetanus elimination efforts, launched in 1989 by the World Health Assembly (WHA), and later expanded in 1999 to include maternal tetanus elimination. The MNTE partnership supports the immunization of women with TT vaccines, through RI strengthening and campaigns in targeted high-risk areas; clean and hygienic birth practices, to prevent mother or newborn infection during birth; and proper postpartum cord care, to prevent umbilical cord contamination. As of June 2015, 38 out of 59 affected countries since 2000 have eliminated MNT (Figure 1).

Figure 1 Countries and Regions having Eliminated MNT Between 2000-2015 (June)

Several types of adult formulation TT/Td are currently available, namely TT vaccines and Td combination vaccines. At present, six manufacturers have WHO prequalified adult formulation TT/Td vaccine, most are in 10 and 20 dose vials (Table 1).

Table 1 WHO Prequalified TT/Td Vaccines (Adult Formulations) – Continued overleaf

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Vaccine</th>
<th>WHO PQ</th>
<th>Presentation</th>
<th>Formul.</th>
<th>VVM</th>
<th>Shelf Life</th>
<th>Cold chain Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>BB-NCIPD (Bulgaria)</td>
<td>TT</td>
<td>2006</td>
<td>10 dose vial</td>
<td>Liquid</td>
<td>Type 14</td>
<td>36 months</td>
<td>4.12 cm³</td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>2006</td>
<td>20 dose vial</td>
<td>Liquid</td>
<td>Type 14</td>
<td>36 months</td>
<td>2.05 cm³</td>
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<tr>
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<td>Td</td>
<td>2006</td>
<td>10 dose vial</td>
<td>Liquid</td>
<td>Type 14</td>
<td>36 months</td>
<td>4.12 cm³</td>
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<td></td>
<td>Td</td>
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<td>20 dose vial</td>
<td>Liquid</td>
<td>Type 14</td>
<td>36 months</td>
<td>2.05 cm³</td>
</tr>
<tr>
<td>Bio Farma (Indonesia)</td>
<td>TT</td>
<td>2003</td>
<td>Unject™ † 1 dose</td>
<td>Liquid</td>
<td>Type 30</td>
<td>24 months</td>
<td>12.00 cm³</td>
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<tr>
<td></td>
<td>TT</td>
<td>1999</td>
<td>10 dose vial</td>
<td>Liquid</td>
<td>Type 30</td>
<td>24 months</td>
<td>2.10 cm³</td>
</tr>
<tr>
<td></td>
<td>Td</td>
<td>1999</td>
<td>20 dose vial</td>
<td>Liquid</td>
<td>Type 30</td>
<td>24 months</td>
<td>0.75 cm³</td>
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<td></td>
<td>Td</td>
<td>2011</td>
<td>10 dose vial</td>
<td>Liquid</td>
<td>Type 30</td>
<td>24 months</td>
<td>2.23 cm³</td>
</tr>
<tr>
<td>Biological E (India)</td>
<td>TT</td>
<td>2012</td>
<td>1 dose vial</td>
<td>Liquid</td>
<td>Type 30</td>
<td>36 months</td>
<td>14.70 cm³</td>
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<td></td>
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<td>2012</td>
<td>10 dose vial</td>
<td>Liquid</td>
<td>Type 30</td>
<td>36 months</td>
<td>3.90 cm³</td>
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<td>2009</td>
<td>20 dose vial</td>
<td>Liquid</td>
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<td>1 dose vial</td>
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</tr>
</tbody>
</table>

5 MNTE defines tetanus elimination as <1 case / 1,000 live births / every district.
### 3. Current Market Situation

#### 3.1. Demand and Forecast

Country demand for TT/Td procured by UNICEF over the period 2005-2014 averaged approximately 150 million doses a year. It ranged from 93 million to 185 million doses comprising supplementary activities and vaccine prioritization in support of 80-100 countries (Figure 2), of which MNTE campaign activities accounted for 20%. TT vaccine share of total UNICEF TT/Td procurement (2005-2014) accounts for 95%. Td vaccine share is gradually increasing as some countries transition from TT to Td.

WHO recommended countries transition from TT to Td vaccines in 2006, to extend and strengthen adult protection against diphtheria, benefitting from tetanus immunization activities through MNTE RI and campaigns.\(^7\) To date (November 2015) most countries in Latin America and Caribbean have transitioned from TT to Td and eliminated tetanus, but 21 high-risk countries (many of which are large populous countries), mostly in Africa and Asia, have yet to do so. UNICEF issued a Programme Instruction in 2011 to encourage all remaining high-risk countries to plan the transition from TT to Td combination vaccines in line with WHO recommendations.\(^8\) Td vaccine demand subsequently increased from 5 million doses in 2011 to reach 18 million doses by the end of 2014, representing a 3.6 fold increase in total volume (Figure 2).

Nevertheless, the rate of increase in Td vaccine demand has been slower than originally forecast. MNTE activities are increasingly country driven and determined by country government decisions on the timing for transition. UNICEF relies significantly on country government forecasts. However, some country decisions on transition remain unclear or uncertain, and forecast accuracy depends on the feasibility of a country government to fund and implement the transition, as they often face competing campaign activities from other vaccine preventable disease control programmes or routine vaccine introductions. Some country vaccine regulatory environments and licensure could also limit access to vaccines, as not all manufacturers have licensed Td vaccines in all countries procuring through UNICEF. UNICEF nonetheless anticipates TT vaccine procurement share to decrease over the long-term, as more and more country transitions take place. UNICEF’s Td forecasts anticipate demand for this vaccine to reach 44.5 million doses during 2015 and possibly as much as 63 million doses by 2017. Nigeria and other large countries transitioning to Td account for most of the projected increases.

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3.2. Supply

UNICEF recently concluded its 2016-2017 TT/Td vaccine tender, and awarded two year LTAs to five manufacturers to supply 165 million TT/Td doses a year during 2016-2017 (Figure 3). The LTAs are to ensure an uninterrupted, sustainable vaccine supply, and secure a wide supplier base to support country transition requirements (Figure 3).

UNICEF split the awards to supply 165 million doses of TT/Td during 2016 equally between the three available multi-dose vial presentations (i.e. 55 million doses per each vaccine: 10-dose Td vaccine; 10-dose TT vaccine; and 20-dose TT vaccine). As many suppliers produce both TT and Td vaccines, UNICEF’s LTA arrangements ensure that overall vaccine supply availability is flexible to absorb uncertainties in the timing of country transition decisions and necessary changes to manufacturer production requirements. Manufacturers require at least 4-months lead-time to switch between vaccine production lines to ensure timely TT and Td vaccine supply availability. UNICEF has left 2017-award allocations generic, and does not identify any specific vaccines (Figure 4).

Source: UNICEF Supply Division.
UNICEF will review specific vaccine allocations for 2017 during 2016, and communicate these to manufacturers during 3Q 2016, allowing them sufficient lead-time to accommodate any changes in accordance with the latest intelligence on country demand, transition requirements and supply timing. UNICEF will review country forecasts each quarter in order to improve country forecast accuracy.

Figure 5 Low-Income and Middle-Income Country TT/Td Procurement through UNICEF 2015

As aforementioned, UNICEF anticipates TT/Td procurement to reach approximately 140 million doses during 2015. As of September 2015, around 70% of this procurement is on behalf of middle-income countries (MIC) (Figure 5). Manufacturers do not make any distinction in pricing between low-income countries (LIC) and MICs. Put another way, all LICs and MICs procuring TT/Td through UNICEF access these vaccines at the same prices irrespective of their average per capita income levels, and irrespective of whether or not they access donor support (e.g. from the Gavi, the Vaccine Alliance) for other vaccine programmes.

Figure 6 UNICEF Td-10 WAP per Dose 2010-2017 (Nominal terms)

TT/Td vaccine weighted average price (WAP) per dose in nominal terms have been relatively stable since 2010. UNICEF anticipates 2016 Td 10-dose vial WAP per dose to decrease by 1.28%, compared to 2015, and remain at US$ 0.11 (Figure 6). UNICEF anticipates 2016 TT 10-dose vial WAP per dose to increase by 14%, compared to 2015 from US$ 0.08 to approximately US$ 0.10. Similarly, UNICEF anticipates an increase of 12% in WAP per dose for TT 20 dose vials in 2016, compared to 2015 to reach US$ 0.06 from US$ 0.055.

Source: UNICEF Supply Division.

4. Issues and Challenges

- Aggregate TT/Td country demand is stable, though country transition decisions from adult TT to adult Td vaccines and the timing of such transitions is uncertain for many countries. This undermines specific vaccine forecast accuracy.
- Manufacturers require at least 4-months lead-time to switch between vaccine production lines to ensure timely TT and Td vaccine supply availability. Large TT/Td procuring countries need to anticipate TT and Td vaccine production switch lead-times when planning transition decisions, to ensure timely supply delivery of the necessary vaccine.
- Some country vaccine regulatory environments and licensure requirements may limit access to some vaccines, as not all manufacturers have licensed Td vaccines in all countries procuring through UNICEF.
5. **Steps Forward**

- UNICEF recently concluded its tender and awarded LTAs in October 2015 to supply 165 million TT/Td doses a year through five suppliers during 2016-2017. The LTAs will ensure sufficient supply to meet overall country requirements, and flexibility to meet country-specific vaccine requirements depending on transition decisions and the associated timing of such transitions.
- UNICEF will review country forecasts on a quarterly basis starting 4Q 2015, to improve forecast accuracy and adjust needs, and will communicate to partners and manufacturers.
- UNICEF will review specific vaccine LTA award allocations for 2017 during 2016 and communicate with manufacturers during 3Q 2016, allowing manufacturers sufficient lead-time to accommodate any changes in accordance with country demand, transition requirements, and timing.

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