GLOBAL MARKET STUDY
DIPHTHERIA & TETANUS CONTAINING VACCINES

Key Takeaways
• WHO recommends for all countries: 1) a life course of six doses of Diphtheria and Tetanus containing vaccines and 2) use of Td in place of TT
• 100/194 countries do not meet these recommendations, but due to conducive circumstances, they are now likely to implement WHO recommendations
• Full implementation of the recommendations would increase global demand for all D&T containing vaccines by ~20%
• Sufficient supply is available to cover both current and future demand for wP / non-pertussis containing vaccines
• Supply of aP-containing vaccines is currently sufficient to support demand from countries where the product is in use; access in additional countries may be problematic
• Countries with only one locally-registered product are at risk of supply shortages, irrespective of the global supply-demand balance

Market Highlights
WHO recommends 6 doses of Tetanus and Diphtheria – 3 DTP-containing doses in infancy plus: i) 1 dose DTP-containing in the 2nd year of life; ii) 1 dose DTP/DdT/Td at 4-7 years; iii) 1 dose Td at 9-15 years. WHO also has a long-standing recommendation to transition from TT to Td. Due to an increasing number of reported outbreaks of diphtheria, increasing recognition of gaps in adult immunity to tetanus, as well as a more enabling environment (second year of life, early primary school, adolescent, and maternal vaccination platforms), implementation of these recommendations by all WHO member states will result in vaccination schedule changes that could lead to product access issues. 115 countries (84% of the global birth cohort) may modify product choice or their EPI schedule for Diphtheria and Tetanus (D&T) containing vaccines to align with WHO policy recommendations (see Figure 1). 46 of those 115 countries are self-procuring and lack access to market information. Additionally, some access issues have been already raised by countries in the European and American regions.

TABLE 1: D&T-CONTAINING PRODUCTS AND GROUPINGS

<table>
<thead>
<tr>
<th>Primary</th>
<th>2YL / Early Childhood Booster</th>
<th>Pre-Adolescence / Adolescence Booster</th>
<th>Pregnancy &amp; Adult Mono Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td>wP:</td>
<td>DTwP-HepB-Hib</td>
<td>DTwP</td>
<td>TT</td>
</tr>
<tr>
<td></td>
<td>DTwP-HepB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>aP:</td>
<td>DTaP-HepB-Hib-IPV</td>
<td>DTaP</td>
<td>Tdap</td>
</tr>
<tr>
<td></td>
<td>DTaP-HepB-IPV</td>
<td></td>
<td>Tdap-IPV</td>
</tr>
<tr>
<td></td>
<td>DTaP-HepB</td>
<td></td>
<td>Tdap-IPV</td>
</tr>
</tbody>
</table>

2 100/194 countries do not have the recommended six dose D&T schedule (83% of the global birth cohort) and 54/194 countries are using TT only (67% of the global birth cohort).
3 Groupings established for analytical purposes, matching as much as possible product utilization in the EPI schedule. Each vaccine product is only present in the group where its use is most common Td and Tdap are also given during pregnancy but for the sake of analysis, only monovalent TT is part of this group. WHO recommends all countries switch from TT to a product containing both tetanus and diphtheria (low dose) for adolescents, adults and pregnant women. As well, Td-IPV and Tdap-IPV can be given to adults.
Global Demand

2017 global demand of all D&T containing vaccines is estimated at 945M doses.\(^4\) DTwP-HepB-Hib (313M, 33%) and TT (252M, 27%) are the most used (out of 16 total vaccine types). Self-procuring countries represent half of global demand (volume). Furthermore, over half of global demand is from the 10 most populous countries.\(^6\)

Evolution of demand up to 2032 was estimated; making assumptions about introduction dates for booster doses and for TT to Td switch, in line with WHO recommendations.\(^7,8\) As a result, total demand is estimated to increase by 20-23.5%, depending on scenarios (linked to possible Gavi support of all three booster doses and optimistic coverage increase assumptions) (see Figure 2). In particular, there is a large volume of additional demand for Td (115-145M) and DTwP (52-67M) (see Figure 3). It should be noted that Bangladesh, Nigeria and Pakistan (three of the most populous countries in the world) are not producing the antigens required for the six-dose schedule. These countries will switch from TT to Td and need to add boosters to their schedule – in total accounting for ~20% of the additional Td demand and ~25% of DTwP.


\(^{5}\) One additional product, DTwP-HepB-Hib-IPV, is available but it is not yet in use. In view of the uncertainty of its use, Gavi support, the availability of IPV and the fact that the vaccines is most likely to replace DTwP-HepB-Hib, no specific demand is included in the forecast.

\(^{6}\) Ten most populous countries, in order: China, India, USA, Indonesia, Brazil, Pakistan, Nigeria, Bangladesh, Russia, Japan.

\(^{7}\) Introduction dates for booster doses were predicted based on a country’s GNI per capita and governance, DTP3 coverage, Diphtheria burden and other planned new vaccine introductions. Global switch to Td by 2022 (India in 2019) is based on advice from a Temporary D&T WHO Advisory Group to WHO.

\(^{8}\) Tetanus vaccine: WHO position paper, Weekly epidemiological record, 10 February 2017.
Global Supply

There are 40\(^{9}\) suppliers of D&T containing vaccines: 35 producers and five distributors; nine have prequalified (PQ’d) products. Five manufacturers have a large portfolio of products (6 to 12 vaccine products) serving the most common schedules.

As presented in table 2, available supply ranges from 400M to 700M doses across the four steps of the schedule (see table 1 for groupings of products).

**TABLE 2: GLOBAL SUPPLY BY PRODUCT GROUP**

<table>
<thead>
<tr>
<th>Product Group</th>
<th>Global Supply 2017</th>
<th>Short-term Additional Capacity**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PQ’d</td>
<td>Non-PQ’d</td>
</tr>
<tr>
<td>TT</td>
<td>330M</td>
<td>210M</td>
</tr>
<tr>
<td>Primary</td>
<td>wP</td>
<td>530M</td>
</tr>
<tr>
<td></td>
<td>aP</td>
<td>*</td>
</tr>
<tr>
<td>Early Childhood Booster</td>
<td>wP/ no aP</td>
<td>170M</td>
</tr>
<tr>
<td></td>
<td>aP</td>
<td>*</td>
</tr>
<tr>
<td>Pre/Adolescent Booster</td>
<td>no aP</td>
<td>310</td>
</tr>
<tr>
<td></td>
<td>aP</td>
<td>*</td>
</tr>
</tbody>
</table>

*Supply information for vaccines where only two major suppliers exist cannot be made available; this is to prevent disclosure of individual manufacturer information and, as a consequence, infringing anti-completion laws. In those cases, supply is estimated by WHO.

**Additional capacity is supply that is either PQ’d or registered in many countries and therefore accessible to several counties.

**Disclaimer:** The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

*Source: MMGH Consulting - Input collected from all large and mid-sized producers (70% of sample). Detailed data provided by wP / no aP producers. Due to legal constraints, aP data extrapolated from publicly available sources.

*Current as of August 2017
Demand-Supply Balance

At this time, supply is sufficient to meet country demand across all vaccine products. Forecasted future supply availability is dependent on the different vaccine types/products:

- Supply of TT will remain unproblematic in view of a declining demand
- Supply of DT and DTwP-containing vaccines will be more than sufficient in the future; able to absorb production issues or changes in the supplier base
- Supply of Td will also remain more than sufficient in the short and mid-term. The demand-supply balance of Td should be revisited in ~10 years, given forecasted demand increase

- There is instead limited flexibility for aP-containing combinations whereby any substantial (10%+) increase in demand, in particular from countries not currently using those products, may result in a high risk of shortages or delays in supply. Additional flexibility can be gained with sufficient warning (12 to 18 months) to manufacturers to allow for adjustments to production planning.

Importantly, as noted in other vaccine markets, more than 60 countries have vaccines in their schedule for which only one product is registered. Those countries may face a higher risk of shortages, irrespective of the global supply situation, in the event of manufacturing issues or market exit by their sole supplier.

**FIG. 4: DEMAND-SUPPLY BALANCE**

1. Lower and upper bounds are MIC private market estimate excluded or doubled, respectively
2. Loss of one major supplier
3. Mid-term: 1 more Penta aP
4. Additional capacity can be activated

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1. DTwP, DTwP-HepB, DTwP-Hib, DTwP-HepB-Hib (Pentavalent vaccine)
2. Source: MMGH Consulting - analysis of product registration based on manufacturers input, Joint Reporting Form (JRF), WHO's analysis of country acceptance of Collaborative Procedure for Registration of PQ'd Products, publicly available information from NRAs
3. Note: y-axes of two graphs are not the same scale
Price

Price seems to be tiered by income group and UNICEF and PAHO almost consistently achieve the lowest prices. aP-containing products are much more expensive than wP, e.g. the average price of DTaP is ~20X more than DTwP and ~4X more than DT (all 1-dose vials). The addition of IPV to the product also increases the cost, e.g. average price of Td-IPV is ~2X more than Td (1-dose vials). The average price reported in Figure 5 is irrespective of vial-size (additional data can be found at http://www.who.int/immunization/v3p).

FIG. 5: 2016 REPORTED PRICE (V3P SOURCE)

Areas for Action

1. WHO will continue to share available information on global supply and demand dynamics for D&T containing vaccines with all interested parties to inform investment and policy decisions.

2. In particular, WHO will survey countries to update estimates of demand, including vaccine type preference. WHO will pay greater attention to Td and aP-containing vaccines, for which supply risks are higher. Information will be proactively shared with manufacturers to guide investments.

3. WHO will work with UNICEF and other immunization partners to ensure a timely adoption of the WHO recommended 6 doses of D&T containing vaccines – via the introduction of the 3 booster doses and the TT to Td switch. WHO and UNICEF will work to ensure adequate and timely evolution of supply in line with demand.

4. WHO will work with relevant stakeholders to enhance visibility around the issue of limited registration of vaccine products and facilitate suitable solutions to the problem of countries with only one product registered.

Data Sources

Demand: historical procurement data (Joint Reporting Form (JRF)/WHO Vaccine Product, Price and Procurement database (V3P) and UNICEF), global demand forecast (Linksbridge/Gates Foundation Global Vaccine Market Model), and input and review from the WHO Temporary Advisory Group of Experts

Supply: manufacturer interviews (including the five PQ'd), PAHO Revolving Fund consultations, UNICEF SD supply updates, JRF/V3P procurement data, and review of published articles and four policy papers concerning supply

Pricing: historical data review (V3P, UNICEF SD, PAHO Revolving Fund)

For more information, contact: vaccinesupply@who.int


15 It is possible that pricing differences are driven by presentation, volume, contract specifications, etc.