Update on Supply of Diphtheria Antitoxin and the Ad-Hoc Working Group on DAT

BACKGROUND

Diphtheria was one of the leading causes of childhood death in the pre-vaccine era[1]. The development of diphtheria toxoid vaccine in 1923 and its subsequent large-scale use in many industrialised countries in the 1940s-1950s provided a significant turning point for diphtheria control. With the inclusion in 1977 of diphtheria toxoid vaccine (D) in WHO's list of recommended immunizations for its Expanded Programme on Immunization (EPI), global incidence of diphtheria dropped significantly from 384,540 cases in 1980 (see fig. 1) to a steady state rate of around 18,000 reported cases since 2006[2]. There has, however, been an increase in the number of cases noted in 2016 to early 2018 due to outbreaks (fig. 2).

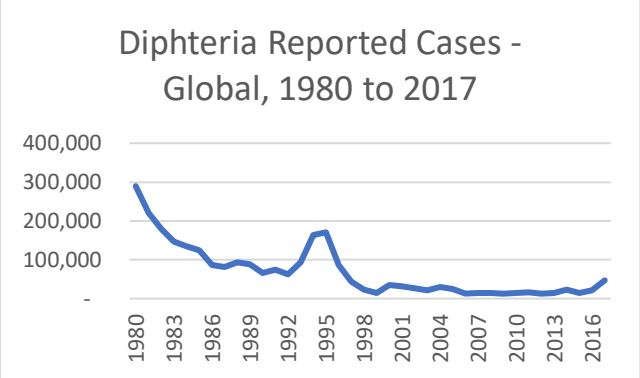


Figure 1: diphtheria reported cases 1980 - 2017[3]

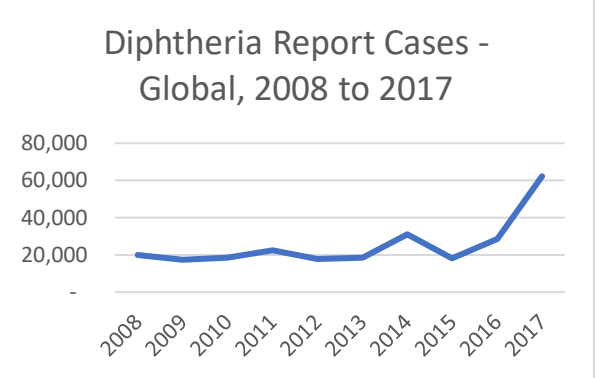
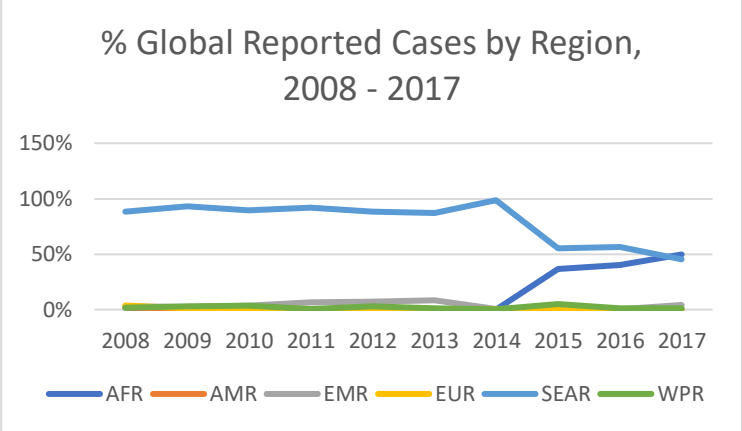


Figure 2: diphtheria reported cases 2008 - 2017[3]

Globally, 76 countries have reported cases of diphtheria at some point in the last 10 years. Of these, the reported cases are systematically concentrated either in a limited number of countries, or are related to outbreaks including Bangladesh, Haiti, Indonesia, Venezuela and Yemen in late 2017 and early 2018.

WHO Region	Nr of Countries reporting diphtheria cases any time from 2008 to 2017
AFRO	14 / 47
AMRO / PAHO	10 / 35
EMRO	11 / 21
EURO	27 / 53
SEARO	7 / 11
WPRO	7 / 27

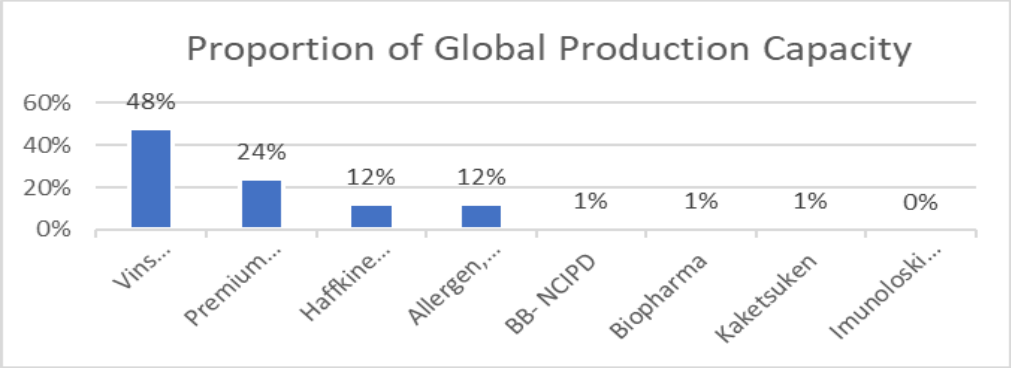


[1] Zakikhany K, Efstratiou A. Diphtheria in Europe: current problems and new challenges. Future Microbiology 2012; 7(5): 595-607.

[2] WHO vaccine-preventable diseases: monitoring system 2018 global summary http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tsincidencediphtheria.html

[3] Source: WHO vaccine-preventable diseases: monitoring system 2018 global summary http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tsincidencediphtheria.html

Until the development and use of diphtheria vaccine, Diphtheria anti-toxin (DAT) was the primary intervention for the treatment of diphtheria. DAT is a biological product obtained by immunizing horses with inactivated diphtheria toxin and subsequently purifying their immunoglobulins. The fall in global incidence of disease has led to a decrease in the supply of DAT, with a number of manufacturers leaving the market and unpredictable demand for remaining suppliers. Analysis carried out by WHO indicates that the total global production capacity is around 83,000 vials, distributed among 8 major manufacturers. Of these, 4 suppliers represent approximately 92% of the global market. Price ranges from around USD 5/vial to USD 1,100/vial.



The WHO Essential Medicines List recommends DAT injection: 10 000 IU; 20 000 IU in vial. The global short-term need for DAT is estimated at around 32,000 vials based on an estimated need for 8,000 treatment courses requiring 40,000 IU, with an average of 5 vials per patient / treatment (from a range of 10,000 – 100,000 IU / treatment)[4].

PROBLEM STATEMENT

With a limited number of suppliers, production lead time, variable product quality and highly fluctuating demand as a result of outbreaks, there is a need to ensure rapid access to DAT for the treatment of diphtheria cases. In light of this, the issue of supply of DAT was considered by SAGE at its meeting in April 2017. SAGE provided the following recommendation to WHO:

"SAGE expressed its grave concern about the limited DAT supplies worldwide, and stressed that DAT is urgently needed for managing suspected cases of diphtheria. SAGE therefore advised that WHO collaborate closely with partners to establish and manage a global procurement mechanism and a physical or virtual DAT stock-pile that would be available to all countries. SAGE further urged that regulatory pathways be established to ensure the rapid deployment of DAT. In the long term, SAGE advised WHO to identify mechanisms to support the development of a monoclonal antibody as an alternative to DAT of equine origin."

Estimating demand for DAT may face three major unknowns:

- total number of cases, including unforeseen outbreak situations
- total product requirement per case (i.e. based on stage at which the treatment is given)

[4] http://www.who.int/immunization/sage/meetings/2017/april/3_Diphtheria_anti_toxin.pdf?ua=1

- product potency; WHO specifications recommend 10,000 IU / vial but product testing indicates that some products show lower potency levels, sometimes reaching only 50% of required levels

An additional consideration issue is the absence of quality assured products compliant with required quality standards. Quality testing of DAT is available and carried out on request at the National Institute of Biological Standard and Control[5] (NIBSC) in the UK and the Paul-Ehrlich-Institute[6] (PEI) in Germany.

Predictability of demand influences not only current production capacity, but also impacts on producers' production plans and investment decisions, including decisions around investment in new products and/or the quality of existing products. Unpredictable demand combined with 4-6 months production lead time highlights the importance of better planning, demand forecasting or establishing regional or global stockpile.

WHO uses a number of different models for global stockpiles; stocks of product may be held at the manufacturer site, at a centralized location (e.g. WHO Headquarters) or at regional level. Possible governance mechanisms include the International Coordination Group[7] (ICG) approach provides a process of making decisions on vaccine allocation for outbreak response when supply is very limited, or the Humanitarian Mechanism[8] (HM), which ensures that defined government, NGO or UN actors responding to emergencies have access to selected vaccines at affordable prices. These different options will be carefully considered to take into account the specificity of DAT, including quality assurance.

WORKPLAN OF THE AD-HOC WORKING GROUP ON DAT SUPPLY

In November 2017, WHO has established an Ad-Hoc Working Group to address this SAGE recommendation. The membership of this working group includes CDC; EMA; European Commission; ECDC; FDA; MSF; MHRA; NIBSC; PAHO; PEI; PHE; UNICEF SD; WHO HQ; WHO Regional Offices. The Terms of Reference are available on the WHO website[9].

The objective of the Working Group follows the priorities highlighted by SAGE. The priorities have been further developed into a workplan as follows:

1) **Short term (2019)**: procurement / contracting with manufacturers to ensure availability of DAT for 2019, product selection criteria, and partner coordination
2) **Medium term (2 to 3-year horizon)**: develop a formal process for quality assessment and supply response option (i.e. stockpile or other solution)
3) **Long term (3 to 5-year horizon)**: availability of new products or improvement of existing options

[5] https://nibsc.org/
[6] https://www.pei.de/EN/home/node.html
[7] http://www.who.int/csr/disease/icg/en/
[8] http://www.who.int/immunization/programmes_systems/policies_strategies/vaccination_humanitarian_emergencies/en/
[9] http://www.who.int/immunization/diseases/diphtheria/en/

1) Short term (2019)

The most immediate concern of the SAGE, the Working Group and countries is to ensure that they have access to sufficient quantities of quality DAT to respond to their needs. Coordinating information is therefore a first step in addressing the situation. In response, WHO has:

- coordinated with partners to identify existing stock on hand, estimated needs and product specifications. Estimated demand for 2019 is 10,000 to 12,000 vials across three major procuring agencies (WHO, PAHO Revolving Fund and MSF), based on historical data notably 2018
- WHO (HQ and Regions) have worked with individual countries to address specific requests for DAT supply, for example facilitating information sharing to countries in SEARO and WPRO
- quality tested DAT supplied by three manufacturers, including potency tests
- continued to work with partners to identify the most appropriate structures for addressing access to DAT in outbreak situations. The Ad-Hoc Working Group is working on two-phased approach, taking into account product quality issues. The first, for the short term, focuses on improved communication around estimated need where the WG has coordinated estimates across members and communicates these to suppliers. The second, a medium-term action, will assess any additional need for a stockpile, taking into account currently available stocks, product specifications and quality components

As indicated above, one of the key issues is to balance the requirements of small, steady state demand versus outbreaks which require more significant volumes in a very short time period. To address this:

- the US Centers for Disease Control (CDC) and WHO are working to develop a risk-assessment tool which seeks to identify areas at risk of outbreaks
- partners, notably WHO, MSF and CDC, are working to improve data collection around the number and outcomes of DAT cases, including patient profiles, product used, clinical outcome and adverse events. A standardized case report form (CRF) has been. It is important to work closely with national authorities and Ministries of Health to facilitate relevant data sharing and respect confidentiality
- the WHO Pre-Qualification team has reviewed WHO assessment reports of DAT manufacturers in the past 5 years (since 1 January 2012). Six of the eight manufacturers have been inspected in this time period for other products. This review will help to plan future good manufacturing practice (GMP) site inspections for DAT producers

Next steps will focus the following activities:

- confirm product specifications for the 2019 procurement cycle
- communicate the 2019 demand estimate to manufacturers in order to ensure sufficient supply
- agree on quality aspects, including potency testing for products procured in 2019 (and beyond)

2) Medium term (2 to 3-year horizon)

The main medium-term concern raised by SAGE and the Ad Hoc Working Group is the absence of quality assured products. Four of the eight current manufacturers have local GMP certification, but there is currently no WHO Pre-Qualification process or quality evaluation for DAT products. The priority over the medium term is therefore to ensure DAT of assured quality is available. To move forward on this process, over the past year WHO has:

- agreed on a short-term plan with the WHO PQ team to carry out inspections for the three manufacturers with the highest production capacities, as well as one new manufacturer which may enter the market in the near future

Next steps including the following:

- standardized potency test using the same reference standard among the suppliers
- WHO will define the minimum product characteristics for DAT, taking into existing International Biological Reference Standards[10] and develop a formal quality assessment process (WHO Pre-Qualification or alternative procedure)
- an inspection schedule shall be defined and implemented with the WHO Pre-Qualification team
- WHO and partners represented through the DAT Ad-Hoc Working Group will define the specifications required of a stockpile, define procurement strategies, and establish an appropriate mechanism, replicating existing models if possible. This mechanism will include a decision making process for DAT allocation, and may include options such as a global or regional stockpile, advance commitments or other alternatives

3) Long term (3 to 5-year horizon)

Research into a new monoclonal antibody has progressed, with one organization ready to start Phase I trials. Defining the regulatory requirements for such clinical trials will be essential for the successful future development of such products. In the long term, WHO and partners will focus on the following:

- understanding and agreeing the requirements for moving new monoclonal antibody products into Phase II and Phase III trials
- working with relevant manufacturers to evaluate the potential for improving the production of fragment antigen binding (Fab) products
- providing technical assistance to existing and potential producers of existing and new products to ensure that these are available within the defined product characteristics including price. Such technical assistance may ultimately lead to technology transfer if required

[10] http://www.who.int/bloodproducts/catalogue/Vacc.pdf?ua=1

Conclusion

Existing production capacity is sufficient to meet steady-state needs for DAT, albeit recognizing the need for a 4-6 lead time in production. Key partners including WHO, MSF and CDC currently have access to total stock of approximately 3,000 vials and will coordinate access to up to an additional 8,000 vials in total for 2019. The Ad-Hoc Working Group will define stockpile requirements, including the quality component, and propose mechanisms to ensure rapid coordination of demand and procurement to address diphtheria outbreak situations from 2019 forward.

The issue of product quality remains a priority, and WHO will prioritise inspections of the main manufacturers and potency test (and one new entrant) in 2019.

This work will be complemented by further progress identifying areas at risk of outbreaks and to collect clinical outcome data in order to better understand product use.

Geneva, 7th September 2018