

Diphtheria anti-toxin (DAT) supply issues: brief review and proposition

Diphtheria anti-toxin (DAT) was the first immunotherapeutic ever used. It was developed in the late 19th century, and until the development and use of diphtheria vaccine, DAT was the primary intervention for diphtheria, reducing case fatality rates from 25-50% in untreated patients to 3% in patients treated earlyⁱ. It is obtained by immunizing horses with inactivated diphtheria toxin, and purifying the immunoglobulins.

During the first half of the 20th century many countries produced DAT for national use, however with the increasing use of vaccine and declining incidence of the disease the market for DAT collapsed, and with it the number of manufacturers. As a result there is no manufacturer producing DAT on a routine basis, and only a few manufacturers have retained the procedures and necessary horse flocks to be able to provide this product (see below).

A few countries have been maintaining stockpiles, however these stockpiles are small and most have either expired or have had the expiry dates extended through re-testing by an independent laboratory to confirm activity of the product. In Europe 60% of member states have reported obtaining DAT supplies even for diagnostics highlighting risksⁱⁱ. Other countries such as South Africa facing small outbreaks, have made requests to manufacturers for supply of a few vials. Effective treatment of cases requires rapid access to and administration of DAT. In the event of a suspected or confirmed case in the absence of a stockpile the time taken to identify a manufacturer with remaining supply within expiry date (if at all available), and the time to arrange for shipment, may mean the supply arrives too late to save the lives of the patients. Regional stockpiles that can be readily accessed may be a preferable solution.

Alternatives to equine-derived DAT:

Human polyclonal DAT is available for diagnostic purposes. While a DAT prepared from blood donations was developed in Australia in the 1970sⁱⁱⁱ there is currently no supply for therapeutic use. Studies during the outbreak in Russia in the 1990s showed that plasma from selected donors amongst convalescent patients could be used^{iv} however this is not a commercial product.

Several groups are developing monoclonal DAT preparations^v including MassBio (USA) which has demonstrated efficacy of their monoclonal in preclinical models. A monoclonal DAT preparation could have significant advantages over equine DAT in that the quality and safety issues associated with equine preparations would be avoided, and in theory supplies could be assured. It will however require several years of clinical development and several million dollars of public-sector funds to bring this product to approval, and the production costs are unlikely to be less than for the equine product. While this may become a useful product in the future it is not currently available.

Manufacturing capacity for equine DAT:

The manufacturers known (through written confirmation) to have current DAT manufacturing capacity (but not necessarily maintaining supplies) are:

India: VINS Bioproducts Ltd.

Premium serums & vaccines Ltd. (which has acquired the SIIL process) .

Brazil: Butantan Institute.

Manufacturers thought to have DAT manufacturing capacity (no reply to written enquiry to date):

Russia: Microgen

Japan: Kaketsuken

Iran: Razi Institute

Potential Needs

The number of reported cases each year and by region are as follows:

Region	2011	2012	2013	2014	2015
AFR	13	27	128	1	1654
AMR	12	2	5	10	49
EMR	352	334	392	40	43
EUR	33	32	33	35	54
SEAR	5179	3953	4080	7666	2504
WPR	37	142	42	22	226

This suggests that an **annual supply of 4000-8000 treatment courses** would be required to enable access for all patients. DAT is administered intravenously in a saline drip over 2-4 hours. Testing for sensitivity to DAT through a scratch test or an ID test must be performed prior to administering DAT. Treatment therefore requires access to appropriate health care infrastructure as well as appropriate diagnostic capacity.

DAT is usually provided as lyophilised immunoglobulin preparation containing 10,000 IU per vial, and treatment requires between 10,000 (for early pharyngeal disease) and 100,000 IU for systemic disease or in patients with diffuse swelling of the neck^{vi}. Assuming an average requirement of 40,000 IU, 8000 treatment courses therefore corresponds to roughly 32000 vials.

Initial discussions suggest that at such a scale the price per vial will be less than \$10 per vial.

Conclusion:

The existing small stockpiles are either depleted or running out, and are largely insufficient to meet the potential needs in low- and middle- income countries. The establishment and maintenance of larger stockpiles is very feasible and several companies are capable of generating sufficient product. However, in order for such a stockpile to be procured by UN agencies prequalification will be required, and to date no equine polyclonal serum has been prequalified. The recent approach to provide an emergency listing for equine-derived anti-snake venom preparations may provide a mechanism for such procurement.

The potential size of such a stockpile needs careful consideration since treatment of diphtheria cases is also dependent on diagnostic capacity and provision of health care services.

ⁱ Naiditch MJ, Bower AG. Diphtheria. A study of 1433 cases observed during a ten year period at the Los Angeles County Hospital. *Am J Med.* 1954;17:229-45

ⁱⁱ ECDC technical Report: Gap analysis on securing diphtheria diagnostic capacity in the EU/EEA. Oct 2016.

ⁱⁱⁱ Hartman LJ. Bioavailability study of diphtheria immunoglobulin (human). *Pathology* 1979. 11(3) 385-7.

^{iv} Bissumbhar B, Rakhmanova AG, Berbers GA, Iakolev A, Nosikova E, Melnick O, et al. Evaluation of diphtheria convalescent patients to serve as donors for the production of anti-diphtheria immunoglobulin preparations. *Vaccine.* 2004;22(15-16):1886-91. <http://dx.doi.org/10.1016/j.vaccine.2003>

^v Huygen K. Development of human monoclonal antibodies to diphtheria toxin: a solution for the increasing lack of equine DAT for therapeutic use? *Virulence*, 2016. 6, 613-5.

^{vi} <https://www.cdc.gov/diphtheria/downloads/protocol.pdf>