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A Review of Adverse Events From the Use of Diphtheria Antitoxin (DAT) in the United States, 2004–2019

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To the Editor—We read with interest the analysis by Eisenberg and colleagues [1] on diphtheria antitoxin (DAT) use during the diphtheria outbreak in Bangladesh, especially with regard to product safety. Eisenberg et al found that administration of a DAT product manufactured by Premium Serum and Vaccines Pvt Ltd (India) was associated with adverse events (AEs) in 170 of 709 (24%) recipients. However, most events were mild, and anaphylaxis occurred in only 3% [1]. Here we provide further evidence on the safety of DAT, administered in a high-resource, non-outbreak setting in the United States.

There has been no US Food and Drug Administration (FDA)–approved DAT product since 1996 [2]. To ensure availability of treatment for suspected diphtheria cases, the Centers for Disease Control and Prevention (CDC) provides DAT, manufactured by Instituto Butantan (IB) (Brazil), under an Investigational New Drug (IND) protocol. The protocol requires treating clinicians to report AEs, defined as any untoward medical occurrences in DAT-administered individuals, whether considered related to DAT or not, to the CDC [3]. The protocol also recommends sensitivity testing prior to DAT administration.

Between 2004 and 2019, 3 lots of IB-manufactured DAT were available for use in the United States. Each lot had an original manufacturer-labeled expiry of 3 years, with the latest expiring in October 2010. Due to the lack of available product globally [4], this supply of DAT has undergone annual or biennial testing to confirm potency, and FDA permitted for expiry extended use under the IND [3].

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Diphtheria antitoxin was administered in 36 patients with suspected diphtheria between 2004 and 2019 in the United States (CDC, unpublished data; [5]). Product administration within the initial 3-year expiration accounted for 47% (17/36) of the administrations, while the remainder was administered under expiry extended use. The age of patients receiving DAT ranged from 6 weeks to 94 years (median age: 47 years). Sensitivity testing was performed on all patients prior to administration; none required desensitization.

Information on AEs was available for 18 of 36 (50%) patients who received DAT and was unknown for the remainder. Among the 18 patients, 11 (61%) received DAT under extended expiry and 7 (39%) received DAT within the expiration. An AE was reported in 1 patient (Table 1), resulting in an AE incidence of 6%. There were no reported cessations of DAT administration due to AEs. Of the 36 DAT recipients, 32 recovered (89%), 3 (8%) died, and 1 (3%) did not have an outcome available. Of the 3 patients who died, all were severely ill prior to DAT administration; their deaths were attributed to causes other than DAT receipt.

Although our sample size was smaller and the setting different, our findings support Eisenberg et al's conclusions on the safety of DAT. In the United States, an AE following DAT administration between 2004 and 2019 was uncommon and mild even with the use of DAT under extended expiry. The lower AE incidence in the United States compared with Bangladesh may be secondary to differences in data-collection methodology and definitions, differences in patient population, or possibly related to the manufacturing origin of the DAT product.

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Table 1.

Adverse Events Reported With Use of Diphtheria Antitoxin in the United States, 2004–2019

DAT Amount Administered	AE Type	Time to AE Following DAT Administration	AE Duration	Treatment Given	Outcome
100 000 IU	• Fever (maximum temperature, 102.5°F) • Maculopapular rash: morbilliform eruption diffusely on the trunk, upper extremities, and lower extremities • Skin biopsy of rash: sparse perivascular lymphatic infiltrate (pathology consistent with drug eruption)	Fever: 90 minutes; rash: 8 days	Fever: 1 hour; rash: 4 days	Acetaminophen (1 g)	Recovered

Abbreviations: AE, adverse event; DAT, diphtheria antitoxin.