Assembly adopted a resolution to eliminate neonatal tetanus by the year 2000; elimination was defined as <1 case/1000 live births in every district in every country. By 1999, elimination was still to be achieved in 57 countries and the deadline was extended until 2005, with the additional target of eliminating maternal tetanus (tetanus occurring during pregnancy or within 6 weeks of its end). Ratification of the Millennium Development Goals, in particular goal 4 (achieving a two-thirds reduction in the mortality rate among children under 5 by 2015), has further focused attention on reducing deaths from vaccine-preventable disease, particularly in the first 4 weeks of life.

Because vaccination reduces the incidence of neonatal tetanus by an estimated 94%, immunization of pregnant women with two doses of tetanus toxoid at least 4 weeks apart has been the primary method of maternal and neonatal tetanus elimination. In some areas, all women of childbearing age have been targeted as a means of increasing vaccination coverage. In addition, educational programs have focused on improving hygiene during the birth process, an intervention that in itself is estimated to reduce neonatal tetanus deaths by up to 40%.

The latest available data show that 34 countries have yet to eliminate maternal and neonatal tetanus, although incidence has declined significantly. Worldwide, deaths from neonatal tetanus fell by 92% between 1990 and 2008; in the latter year, with 84% of newborns protected from the disease by maternal vaccination, there were an estimated 59,000 neonatal tetanus deaths. Despite this relative success, immunization programs need to be ongoing as there is no tetanus herd immunity effect and *C. tetani* contamination of soil and feces is widespread.

178 Botulism

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Botulism, recognized at least since the eighteenth century, is a neuroparalytic disease caused by botulinum toxin, one of the most toxic substances known. While initially thought to be caused only by the ingestion of botulinum toxin in contaminated food (food-borne botulism), three additional forms caused by in situ toxin production after germination of spores in either a wound or the intestine are now recognized worldwide: wound botulism, infant botulism, and adult intestinal colonization botulism. In addition to occurring in these recognized natural forms of the disease, botulism symptoms have been reported in patients receiving injections of botulinum toxin for cosmetic or therapeutic purposes (iatrogenic botulism). Moreover, botulism was reported after inhalation of botulinum toxin in a laboratory setting. All forms of botulism manifest as a relatively distinct clinical syndrome of symmetric cranial-nerve palsies followed by descending bilateral flaccid paralysis of voluntary muscles, which may progress to respiratory compromise and death. The mainstays of therapy are meticulous intensive care and treatment with antitoxin as soon as botulism is suspected and before other illnesses have been ruled out.

ETIOLOGY AND PATHOGENESIS

Seven serologically distinct confirmed serotypes of botulinum toxin (A through G) have been confirmed. Botulinum toxin is produced by four recognized species of clostridia: *Clostridium botulinum, Clostridium argentinense, Clostridium baratii,* and *Clostridium butyricum*. Certain strains may produce more than one serotype. All are anaerobic gram-positive organisms that form subterminal spores; *C. botulinum* and *C. argentinense* spores have been recovered from the environment. The spores survive environmental conditions and ordinary cooking procedures. Toxin production, however, requires a rare confluence of product storage conditions: an anaerobic environment, a pH of >4.6, low salt and sugar concentrations, and temperatures of >4°C. Although commonly ingested, spores do not normally germinate and produce toxin in the adult human intestine.

Food-borne botulism is caused by consumption of foods contaminated with botulinum toxin; no confirmed host-specific factors are involved in the disease. *Wound botulism* is caused by contamination of wounds with *C. botulinum* spores, subsequent spore germination, and toxin production in the anaerobic milieu of an abscess or a wound. *Infant botulism* results from absorption of toxin produced in situ by toxigenic clostridia colonizing the intestine of children ≤1 year of age. Colonization is thought to occur because the normal bowel microbiota is not yet fully established; this theory is supported by studies in animals. *Adult intestinal colonization botulism,* a very rare form that is poorly understood, has a pathology similar to that of infant botulism but occurs in adults; typically, patients have some anatomic or functional bowel abnormality or have recently used antibiotics that may help toxigenic clostridia compete more successfully against the normal bowel microbiota. Despite antitoxin treatment, relapse due to intermittent intraluminal production of toxin may be observed in patients with adult intestinal colonization botulism.

Regardless of how exposure occurs, botulinum neurotoxin enters the vascular system and is transported to peripheral cholinergic nerve terminals, including neuromuscular junctions, postganglionic parasympathetic nerve endings, and peripheral ganglia. Botulinum toxin is a zinc-endopeptidase protein of ~150 kDa, consisting of a 100-kDa heavy chain and a 50-kDa light chain. Steps in neurotoxin activity include (1) heavy-chain binding to nerve terminals, (2) internalization in endocytic vesicles, (3) translocation of the light chain to cytosol, and (4) light-chain serotype-specific cleavage of one of several proteins involved in the release of the neurotransmitter acetylcholine. Inhibition of acetylcholine release by any of the seven toxin serotypes results in characteristic flaccid paralysis. Recovery follows sprouting of new nerve terminals.

All botulinum toxin serotypes have been demonstrated to cause botulism in nonhuman primates. Human cases associated with serotypes A, B, E, and F are reported each year. Serotype A produces the most severe syndrome, with the greatest proportion of patients requiring mechanical ventilation. Serotype B appears to cause milder disease than type A in both food-borne and infant botulism. Serotype E, most often associated with foods of aquatic origin, produces a syndrome of variable severity. The rare cases of illness caused by toxin serotype F, whether in infants or adults, are characterized by rapid progression to quadriplegia and respiratory failure but also by relatively rapid recovery. Recent studies have shown that at least some serotypes can be differentiated into subtypes through neurotoxin gene sequencing; however, the impact of these subtype differences on clinical illness is not yet known.

EPIDEMIOLOGY

Botulism occurs worldwide, but the number of cases reported varies among countries and regions. The variation may be due not only to actual differences in incidence but also to (1) availability of resources to identify botulism, a rare disease; (2) differences in reporting requirements; and (3) limited external access to data collections. There is no universal surveillance system to capture worldwide botulism incidence. However, 30 countries currently participate in voluntary reporting of botulism cases to the European Union through an established surveillance system that includes standardized case definitions similar to those used in the United States and Canada. Other countries (e.g., Argentina, China, Thailand, Japan) maintain independent botulism surveillance.

Food-Borne Botulism From 1899 to 2011, 1225 food-borne botulism events (single cases or outbreaks) were reported in the United States; from 1990 to 2000, a median of 23 cases were reported annually. Most such events (~80%) involve vegetables or fish/aquatic animals, usually home-preserved (canned, jarred). Native communities in both the United States (Alaska) and Canada have a high incidence of food-borne botulism due to traditional food-preparation practices; 85% of all cases in Canada occur in Native communities. Outbreaks typically involve two or three cases; however, one restaurant-associated outbreak in 1977 affected 59 persons. Worldwide, the highest incidence rate is reported from Georgia and Armenia in the southern Caucasus region, where illness is also associated with home-canning practices. Outbreaks in Asia are