



Infant Botulism: Epidemiology, Clinical Features and Treatment

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Disclosures

Ms. Payne has no relevant financial interests or commercial relationships to disclose.

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Objectives

At the conclusion of this presentation, participants will be able to:

- Describe the typical clinical features of infant botulism
- Identify key epidemiological features of infant botulism
- Understand basic laboratory aspects of infant botulism testing and specimen submission
- Describe the process for obtaining clinical consultation and Human Botulism Immune Globulin (BIG-IV or BabyBIG®) from the California Infant Botulism Treatment and Prevention Program (IBTPP)



Outline

- What is infant botulism?
- Epidemiology of infant botulism
 - Geographic distribution
 - Age distribution
 - Exposures
- Infant botulism testing
- Treatment of infant botulism and the IBTPP

What is infant botulism (IB)?

- Temporary intestinal colonization by *Clostridium botulinum*, spore-forming obligate anaerobe
- Affects infants less than 1 year of age
- A rare disease, but most common form of human botulism in the US for more than 30 years
- Symptoms include generalized muscle weakness, with airway and swallowing difficulties
 - Affected infants require hospitalization for feeding and breathing supportive care. Approximately ½ of patients need ventilator care in pediatric ICUs.

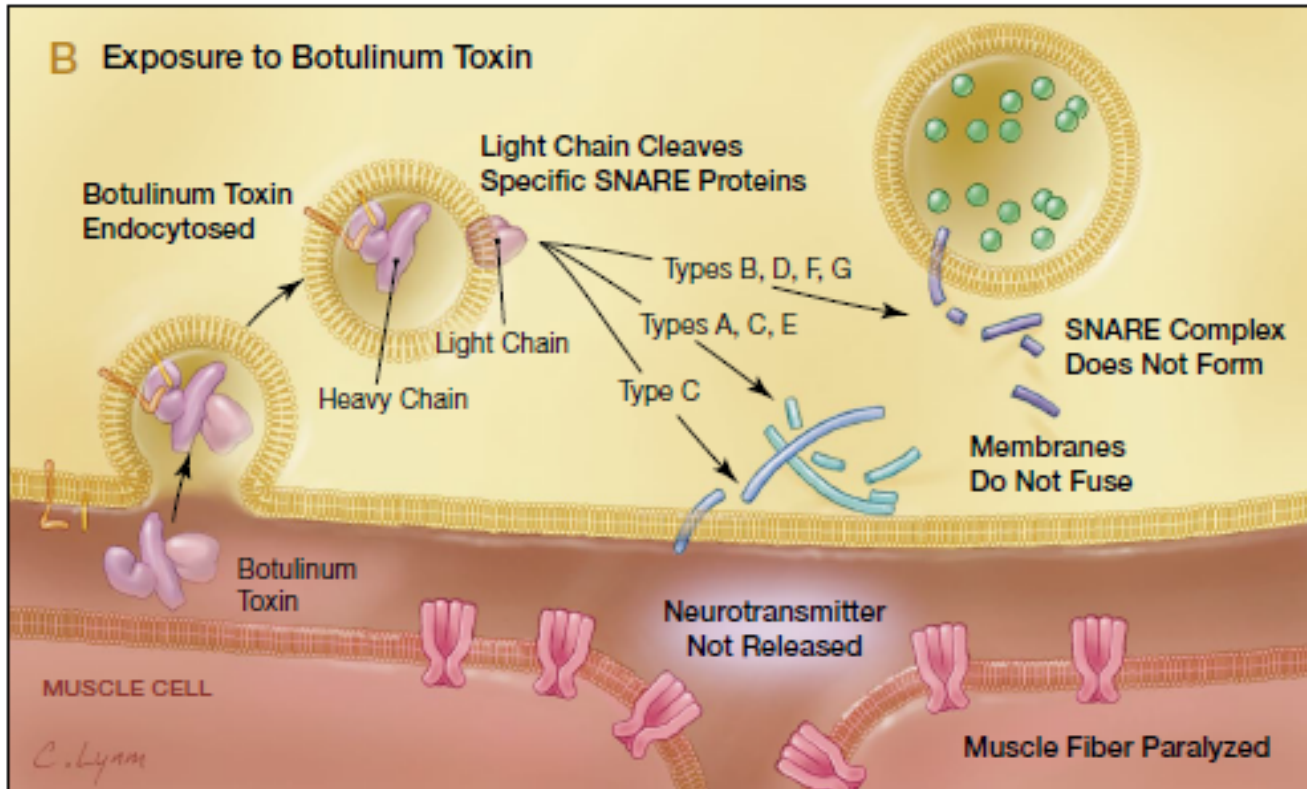


Pathophysiology

- Swallowed spores germinate, then temporarily colonize and produce botulinum neurotoxin (BoNT) in the large intestine
- BoNT is absorbed; carried by bloodstream
- BoNT binds to peripheral cholinergic nerve endings
- BoNT cleaves key intracellular proteins necessary for acetylcholine release resulting in flaccid paralysis
- BoNT does not cross blood-brain barrier

BoNT mechanism of action

Figure 1. Mechanism of Action of Botulinum Toxin



Arnon SS, Schechter R, Inglesby T, Henderson D, Bertlett J, Ascher M, et al.
Botulinum toxin as a biological weapon: medical and public health management.
JAMA. 2001;285(8):1059-70.

Clinical insights

- IB presents as a descending, symmetrical, flaccid paralysis with bulbar palsies in previously well infants
- The clinical spectrum of IB ranges from very mild, outpatient cases to severe/fulminant/SIDS-like presentation*
- A complete recovery expected, in the absence of complications
- Treatment consists of meticulous supportive care (respiratory and feeding support) and antitoxin (BabyBIG®) administration

*Mitchell, W. G. and L. Tseng-Ong. "Catastrophic presentation of infant botulism may obscure or delay diagnosis." Pediatrics 116.3 (2005): e436-e438.

*Nevas, M., et al. "Infant botulism acquired from household dust presenting as sudden infant death syndrome." J Clin Microbiol 43.1 (2005): 511-13.



Presenting characteristics

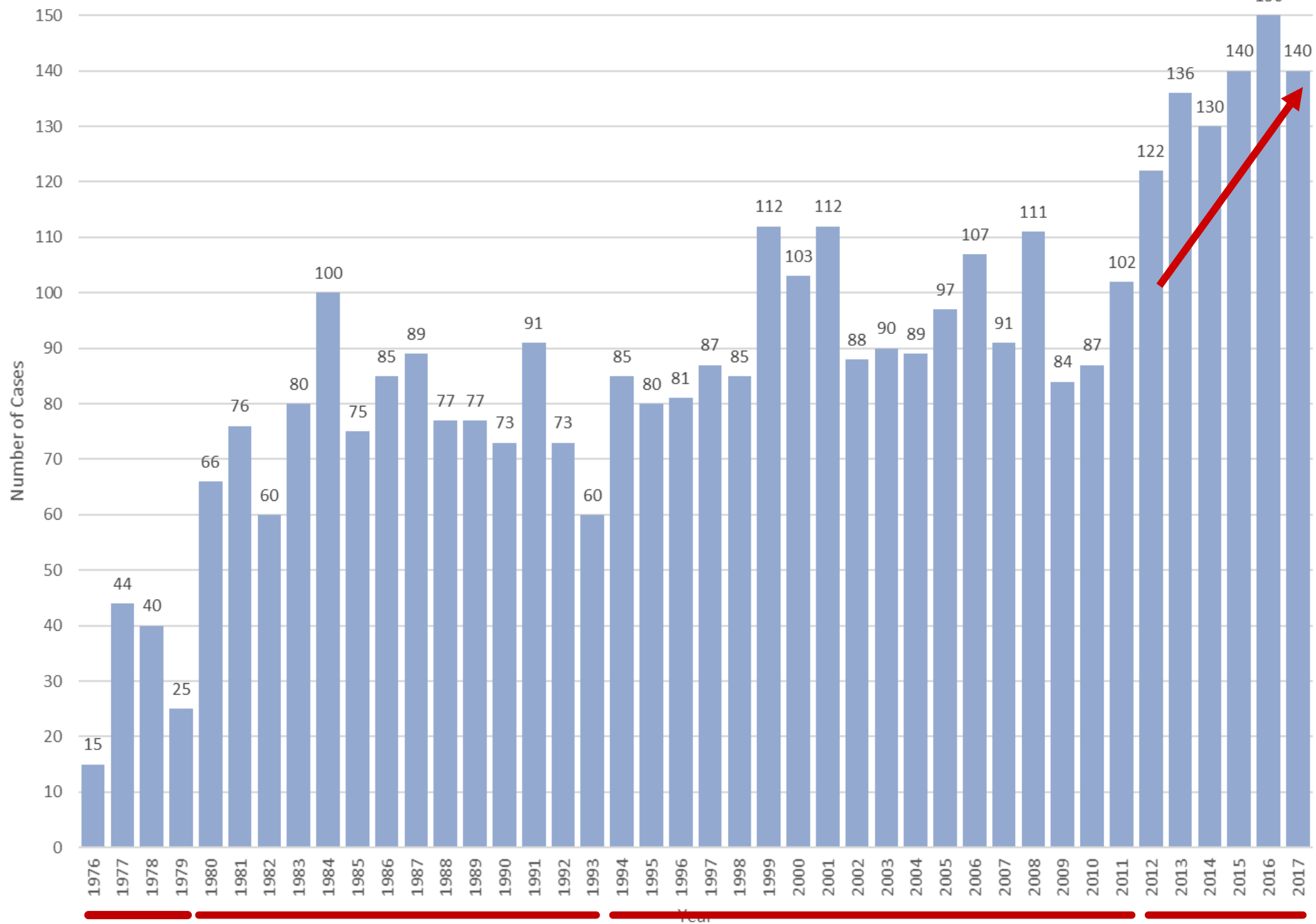
Percent of infant botulism patients reported as presenting with these symptoms, California 1992 - 2017 (N=784)

	Yes	No	Unknown
Generalized weakness	97%	2%	1%
Decreased head control	96%	2%	3%
Poor suck	94%	3%	3%
Constipation	89%	8%	3%
Difficulty swallowing	77%	17%	7%
Sluggish pupils	49%	35%	16%
Respiratory difficulty	31%	67%	2%
Honey exposure	5%	93%	2%

Epidemiology of infant botulism

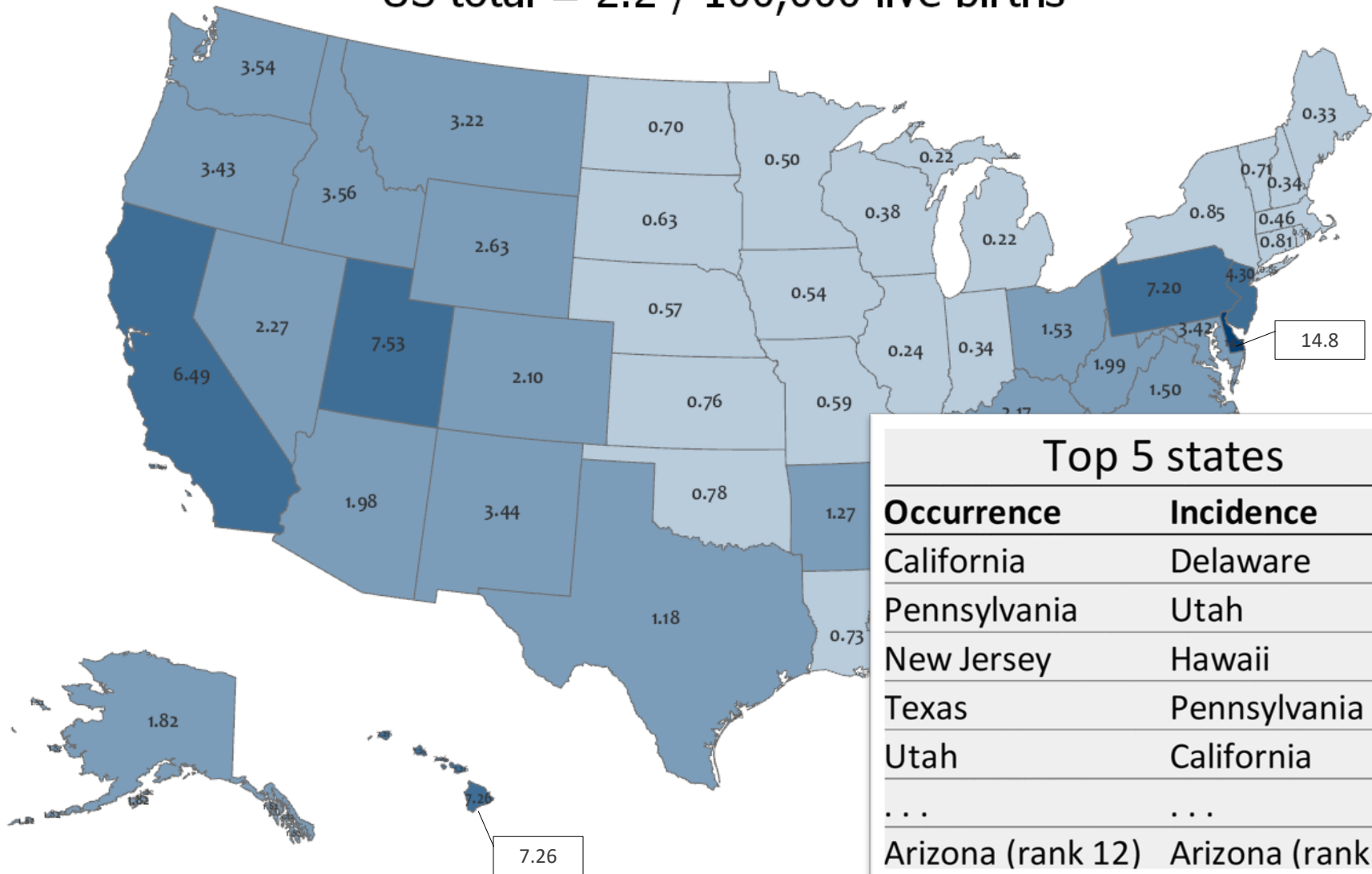
- 3715 US lab-confirmed cases IB cases 1976-2017
- 49.6% Female, 50.3% Male, 0.1% Unknown
- Cases in all major racial and ethnic groups
- Occurrence in all 50 US states & Washington DC
- Caused by strains producing A, B, E, F, Ab, Ba and Bf botulinum toxins

Infant botulism in the United States, 1976 - 2017



US incidence of infant botulism per 100,000 live births, 1976 - 2016

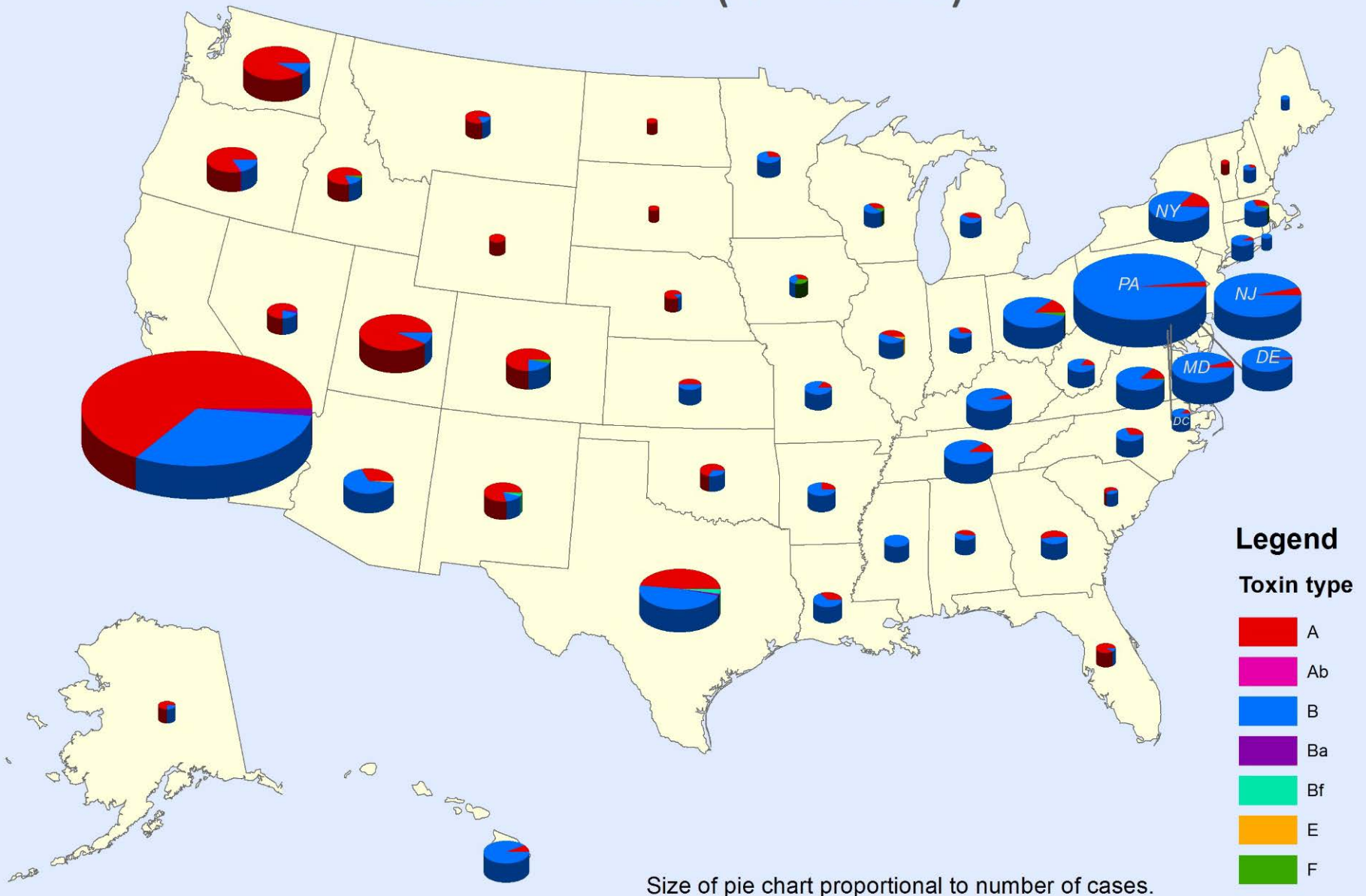
US total = 2.2 / 100,000 live births



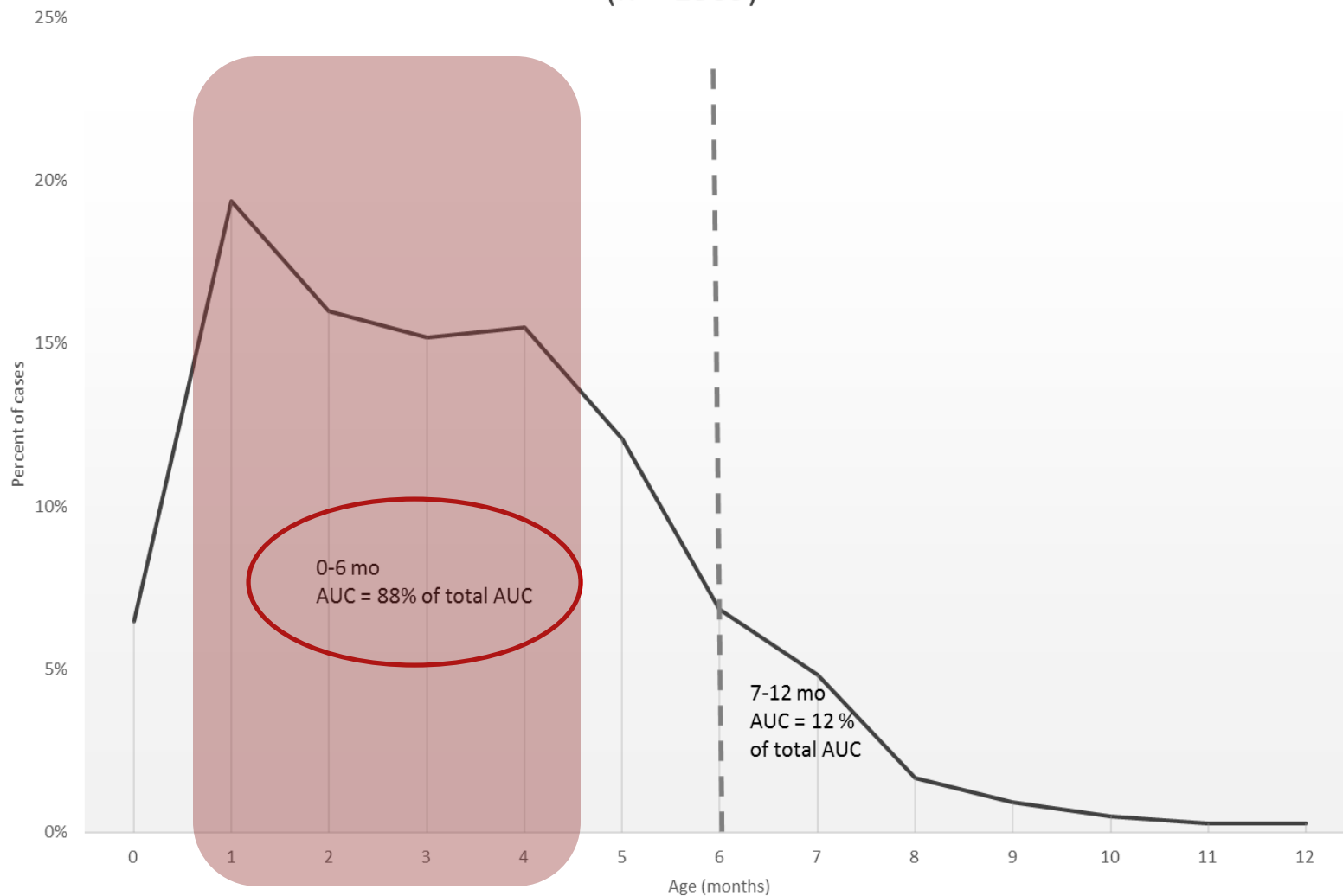
Top 5 states

Occurrence	Incidence
California	Delaware
Pennsylvania	Utah
New Jersey	Hawaii
Texas	Pennsylvania
Utah	California
...	...
Arizona (rank 12)	Arizona (rank 18)

US infant botulism cases, by toxin type, 1976-2017 (n = 3713)



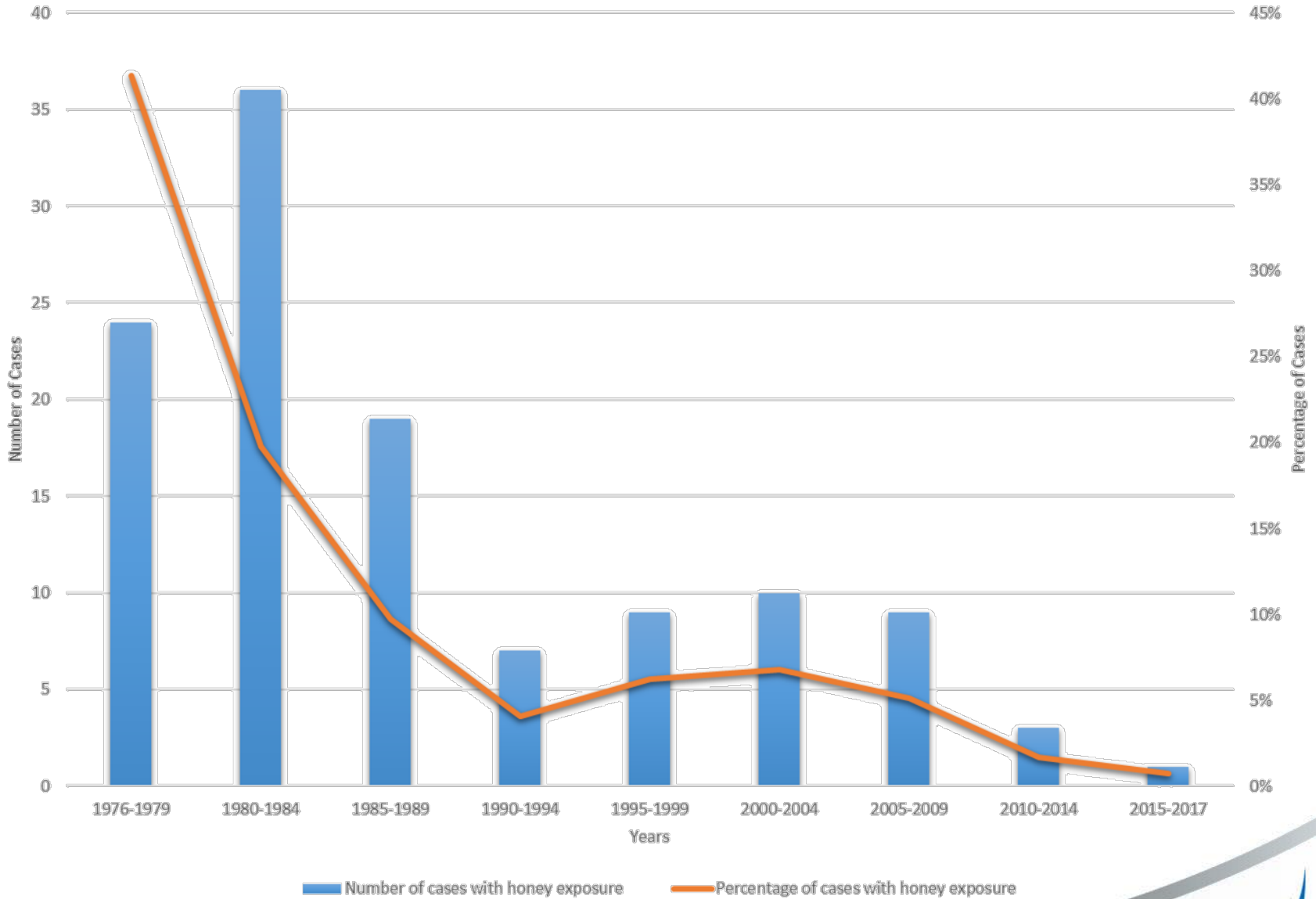
Age distribution for California infant botulism patients, 1976 - 2017 (n = 1389)



Exposures

- *C. botulinum* is a soil-dwelling, spore-forming bacterium found in soils throughout the world
- Soil disturbance (e.g., construction) may make more spores available in the immediate environment
- Most patients likely acquire spores by swallowing microscopic dust particles on which the spores travel
- Honey is the one identified and avoidable food reservoir of *C. botulinum*, and is not a necessary food for infants

Infant botulism patients with honey exposure, California, 1976 - 2017

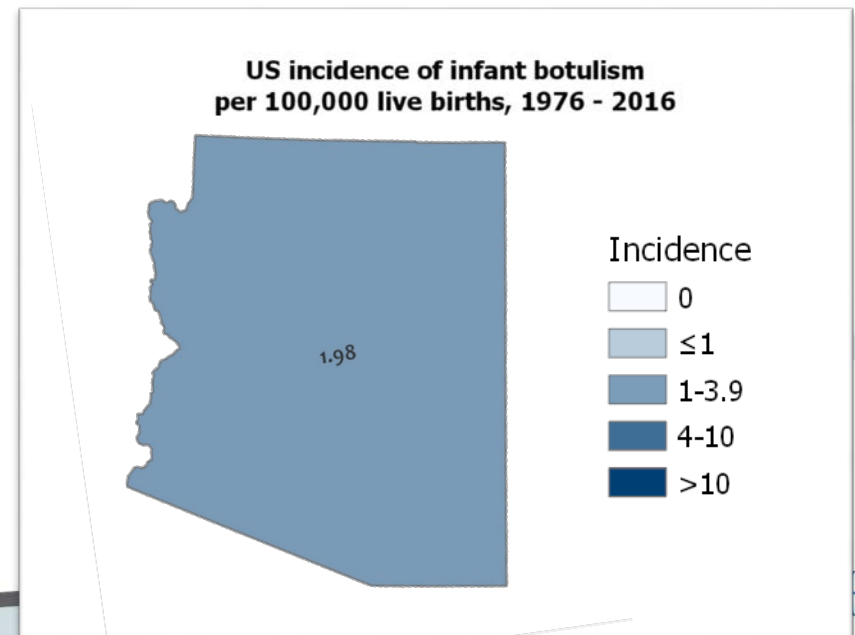


Infant botulism in Arizona

AZ infant botulism cases by county, 2000-2018 (YTD)

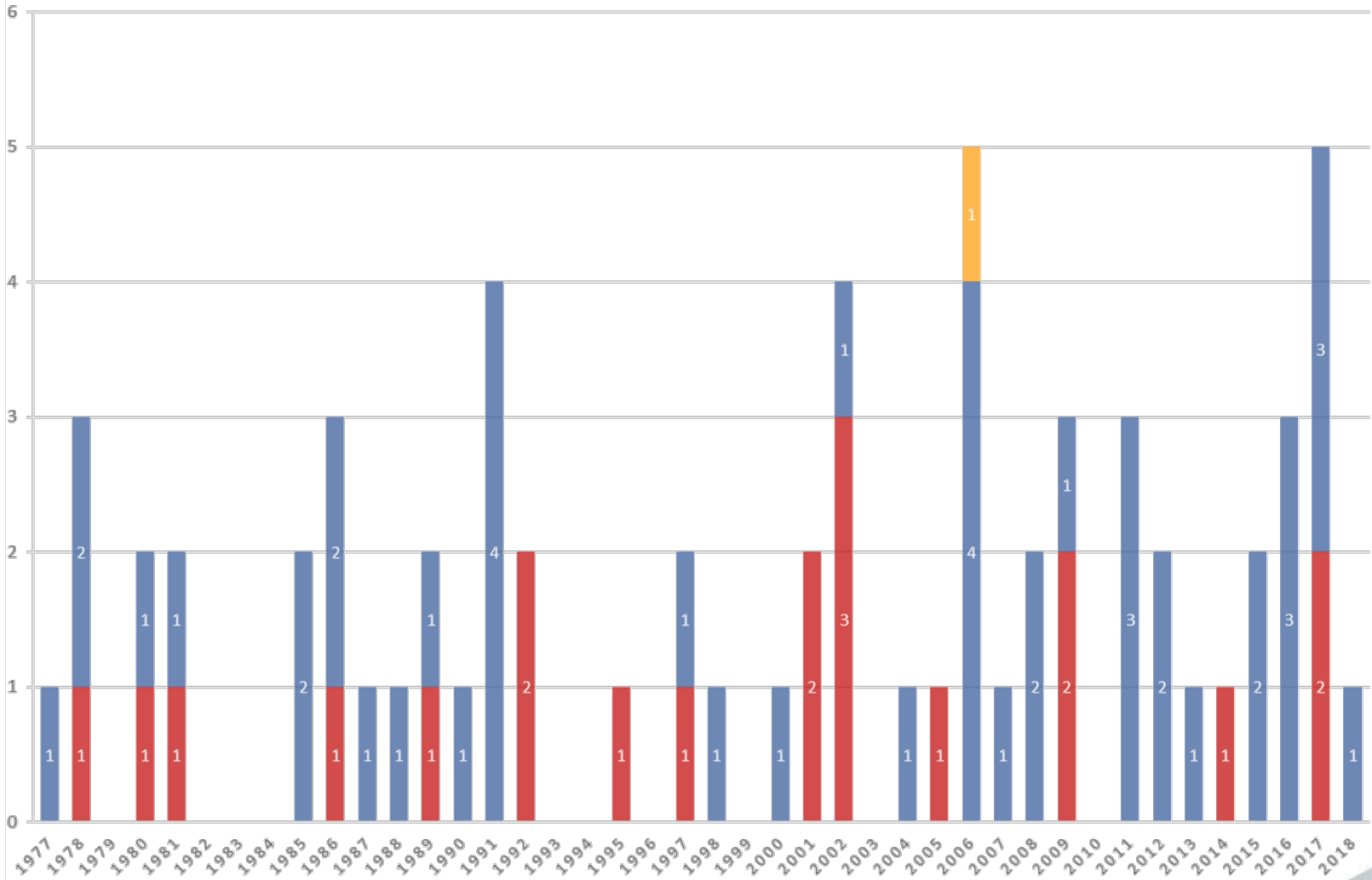


County	Toxin Type			Total
	A	B	E	
APACHE		2		2
COCONINO	1			1
MARICOPA	6	19	1	26
MOHAVE	3			3
PIMA		4		4
PINAL	1	1		2
Total	11	26	1	38



Arizona infant botulism cases, by toxin type, 1977-2018 (ytd)

■ Toxin A ■ Toxin B ■ Toxin E



Infant botulism testing

- Botulism stool/enema testing required for all infants treated with the antitoxin BabyBIG[®]
- Specimens for AZ infants are sent through AZ DPH to CDC's botulism diagnostic laboratory
- Case definition = detection of *C. botulinum* or BoNT in the feces or enema from a symptomatic infant
- Serum is not a reliable specimen for infant botulism testing
- Fecal specimens can be collected before or after antitoxin administration

Infant botulism testing, cont.

- The current “gold-standard” test for infant botulism is the mouse bioassay for detection of BoNT
- Specimens are also often cultured to isolate *C. botulinum*
- Molecular methods including PCR and mass spectrometry may also aid in the diagnosis

BabyBIG for the treatment of IB

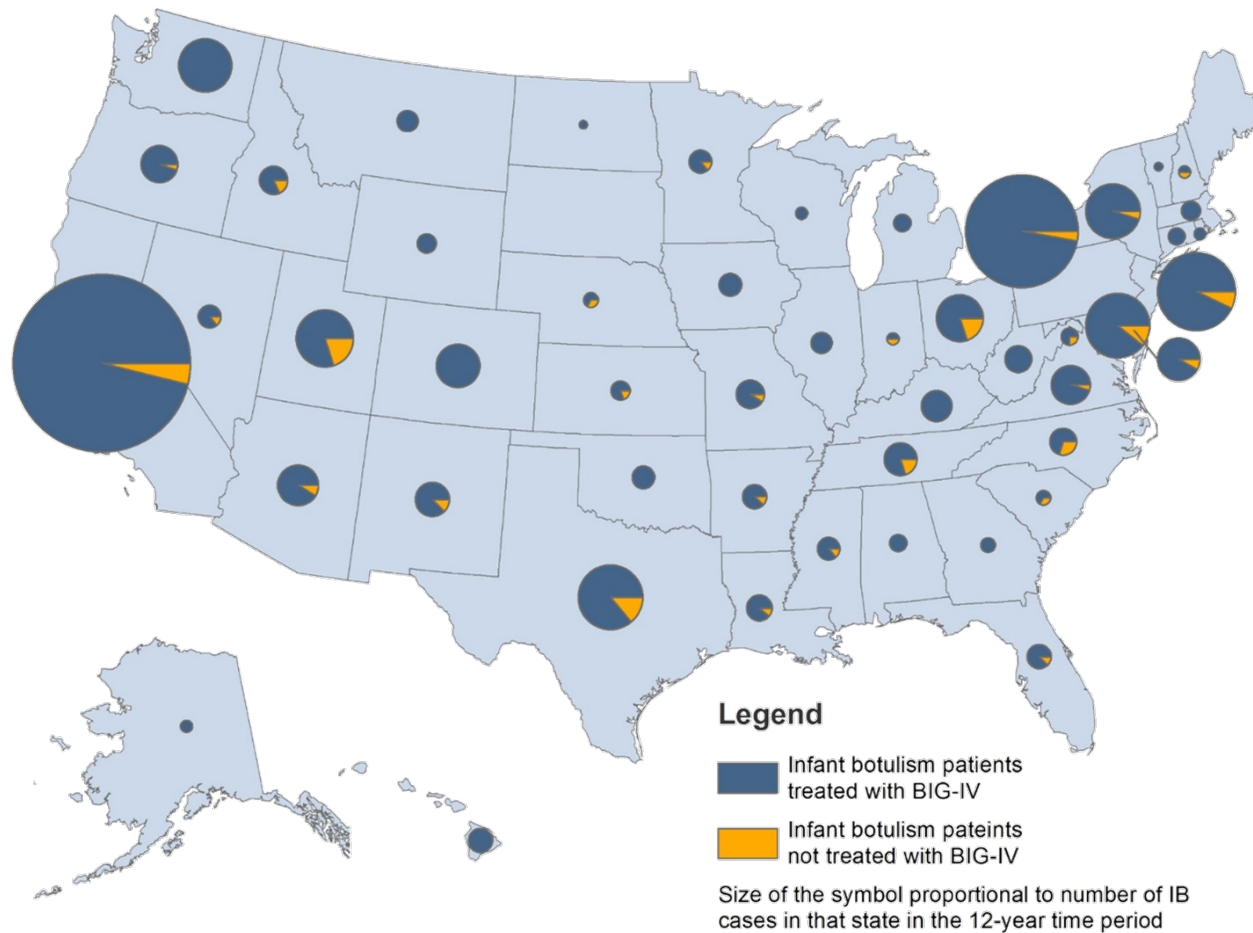
- BabyBIG is a public-service, orphan drug available through consultation with IBTPP
- Human antitoxin/IgG
- In-vivo half-life of 28 d
- Protective for 5+ mo following single infusion
- Neutralizes circulating toxin; does not reverse existing paralysis; early treatment maximizes efficacy
- Enables more rapid recovery and thereby results in shorter length of hospital stay and reduced hospital costs*



*Payne JR, Khouri JM, Jewell NP, Arnon SS. Efficacy of Human Botulism Immune Globulin for the Treatment of Infant Botulism: The First 12 Years Post Licensure. J Pediatr. 2018;193:172-7.

Arnon, S. S., et al. "Human Botulism Immune Globulin for the treatment of infant botulism." N Engl J Med 354.5 (2006): 462-71.

US BabyBIG usage, 2003-2015



Payne JR, Khouri JM, Jewell NP, Arnon SS. Efficacy of Human Botulism Immune Globulin for the Treatment of Infant Botulism: The First 12 Years Post Licensure. *J Pediatr.* 2018;193:172-7.

BabyBIG efficacy

Reductions in Hospital Stay and Costs Achieved with BIG-IV (BabyBIG[®]) Treatment of U.S. Infant Botulism Patients During its Pivotal Phase 3 Trial and, its 12 years Post-Licensure*

	N	Mean Stay (wks)	Hospital Stay Avoided with BIG-IV Use		N	Mean Costs [‡]	Hospital Costs Avoided with BIG-IV Use [‡]	
			Mean (wks)	Total (yrs) [§]			Mean	Total [§]
Placebo group for phase 3 trial (CA) [†]	63	5.7	–	–	63	\$207,500	–	–
Infant botulism patients treated with BIG-IV during the phase 3 trial (CA)	59	2.6	3.1	3.5	59	\$95,200	\$112,300	\$6,624,600
Infant botulism patients treated with BIG-IV in the first 12 years post-licensure (U.S.)	1133	2.2	3.6	66.9	1123	\$118,600	\$88,900	\$86,201,700

*Treated in the U.S. within 7 days of hospital admission. Only patients with type A or B illness included.

[†]Reference group comprised of pivotal clinical trial placebo-treated patients 1992-97. Length of stay numbers rounded to the nearest tenth.

[‡]All costs adjusted to year 2015 dollars and rounded to the nearest \$100. Length of hospital stay data and actual cost data available for >99% of patients.

[§]Totals are calculated separately for patients with type A and type B illness and then summed for the cumulative total; hence, Total (yrs) is not the product of the N x Mean Stay Avoided (wks).

Adapted from: Payne JR, Khouri JM, Jewell NP, Arnon SS. Efficacy of Human Botulism Immune Globulin for the Treatment of Infant Botulism: The First 12 Years Post Licensure. J Pediatr. 2018;193:172-7.



What is the IBTPP?

A program of the CA Department of Public Health that:

- Produces, maintains, stores and distributes BabyBIG[®] to all U.S. infant botulism cases and occasionally internationally (avail. 24/7/365 www.infantbotulism.org)
- Provides infant botulism consultation services to all physicians, hospitals, state and local health jurisdictions, laboratories and parents nationwide
- Investigates all cases of suspected infant botulism and related illnesses in CA with both laboratory and epidemiological methodologies





Questions?

