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Seven-Year Case-Control Study in California of Risk Factors for Infant Botulism

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Objective To ascertain possible risk factors for infant botulism, the intestinal infectious form of human botulism, in the years immediately following its initial recognition in California in 1976.

Study design Parents of 159 California laboratory-confirmed cases of infant botulism from 1976 to 1983 and 318 healthy controls were interviewed using a comprehensive (>300 factors) questionnaire. "Neighborhood controls" (n = 184) were matched on date of birth, sex, race/ethnicity, and neighborhood of residence. "County controls" (n = 134) were matched only on date of birth, sex, and county of residence. Age-stratified bivariate and multivariate conditional logistic regression analyses were performed using SAS.

Results All cases required hospitalization. Bivariate analyses identified several risk factors that in multivariate analyses were not significant. In multivariate analyses, risk factors differed with stratification by age. For the ≤2 month-old neighborhood controls comparison, birth order >1, cesarean delivery, ≤1 bowel movements (BMs) per day, and windy residence area were associated with illness hospitalization, and for the county controls comparison, only pacifier use was associated. For the <2 month-old neighborhood controls comparison, <1 bowel movements (BMs) per day, cesarean delivery, birth order >1, and windy residence area were associated with illness hospitalization, and for the county controls comparison, pets in the home was an additional risk factor.

Conclusions With the exception of the ≤2-month-old county controls group, slower intestinal transit time (≤1 BM/d) was associated with illness. Otherwise, our case–control investigation identified few physiologic, environmental, and maternal factors associated with infant botulism hospitalization in California. *(J Pediatr 2020;227:258-67)*.

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Infant botulism is the uncommon, potentially life-threatening intestinal toxemia that results when ingested spores of *Clostridium botulinum* (or rarely, neurotoxigenic *C butyricum* or *C baratii*) germinate in the lumen of the large intestine and produce botulinum neurotoxin (BoNT).[1-15] After absorption, BoNT blocks the release of acetylcholine from peripheral cholinergic synapses, causing muscle weakness and flaccid paralysis. Patients typically present with constipation, hypotonia, and bulbar palsies (eg, ptosis, ophthalmoplegia, expressionless face, difficulty swallowing, decreased gag reflex, and weak cry).

Modern recognition of infant botulism as a novel infectious disease occurred in California in 1976,[16-18] at which time the present-day California Department of Public Health (CDPH) promptly began a case–control study to identify factors associated with illness hospitalization. All patients were sufficiently paralyzed so as to require hospitalization. Risk factors for the study were chosen because of their possible influence on the intestinal microbiome that *C botulinum* temporarily colonizes in causing infant botulism. Study data analysis was delayed by the development, licensing, and ongoing distribution (1985-present) of the public service (ie, not-for-profit) orphan drug Human Botulism Immune Globulin (BabyBIG) for the treatment of infant botulism.[19-21]

Methods

Cases were defined as hospitalized patients between birth and 1 year of age who presented with an illness consistent with the known paralyzing action of BoNT, in which *C botulinum* organisms or BoNT were identified in a fecal or enema specimen. Illness onset was defined as the date on which the parent or caregiver

BM	Bowel movement
BoNT	Botulinum neurotoxin
CDPH	California Department of Public Health

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first contacted a medical provider regarding symptoms of illness. The incubation period was considered to be the 3-30 days before illness onset.[22]

Only breastfed cases were defined as those infants for whom breastmilk constituted 100% of their milk intake. Similarly, only formula-fed cases were defined as those infants for whom formula milk constituted 100% of their milk intake. Primarily breastfed cases were defined as those infants for whom breastmilk constituted two-thirds or more of their total milk intake. Similarly, primarily formula-fed cases were defined as those infants for whom formula milk constituted two-thirds or more of their total milk intake. Breastfed-at-onset cases were defined as those infants who were still receiving breastmilk at illness onset. These definitions applied only to the infant's milk-feeding experience without regard to other foods, if any, that the infant may have been fed.

Because infant feeding practices differ by infants' age, data were stratified by age-at-onset of illness. For each food category, any intake was defined as any consumption between birth and illness onset. Consistent intake of any food category was defined as exposure ≥3 times during any 4-week period between birth and illness onset. Race/ethnicity was categorized as White, Asian, Black, other races (American Indian, Alaska Native, Native Hawaiian, and Multiple Races), and Hispanic. Dust exposure was defined as any of the following: neighborhood construction, farming, street excavation, landscaping, ditch digging, gardening by the parents, or maternal/paternal occupational contact with soil.

Patients and Controls

The study was approved by the institutional review board of the State of California and conducted in accord with guidelines and regulations for the protection of human subjects. All infants with laboratory-confirmed infant botulism in California between February 1976 and March 1983 were included, except for the year 1979, when funding and staffing shortages interrupted the study. Only 9 cases of infant botulism were reported in CA in 1979. Suspect cases were referred to CDPH by attending physicians and/or county health departments. Laboratory testing at CDPH used the standard mouse bioassay to identify BoNT and established microbiological methods to isolate *C botulinum*.[23,24]

While the patient was still hospitalized, 10 potential control infants born within 14 days of the case who met the matching criteria (see below) were identified from county birth records. Parents of potential controls were telephoned, and the first 2 families who agreed to participate were interviewed. For the first 25 cases, the 2 control infants were matched on date of birth (ie, age), sex, race/ethnicity, and place of residence (living <3.2-km [2-mile] radius of the case), designated as "neighborhood controls." In geographically large counties with more dispersed populations, controls meeting the birth date criterion were selected from the closest residing infants. However, it soon became evident from field observation that matching the neighborhood controls on race/ethnicity and nearby place of residence created a de facto match for socioeconomic status. Because socioeconomic status is associated with type of infant milk feeding (breast or formula),[25-29] and because type of milk feeding influences the composition of the gut microbiome,[30-33] the criteria for selecting the second control infant were modified. After the first 25 cases and their controls had been enrolled, for the subsequent 134 cases the second control was matched as before on date of birth and sex, while the neighborhood of residence criterion was changed to county of residence and the matching on race/ethnicity was discontinued. This modified second control infant was designated the "county control" (**Figure 1**; available at www.jpeds.com).

Interview and Questionnaire

Case and control parents were promptly interviewed in person by trained interviewers who were either physicians, nurses, or epidemiologists. Comprehensive data were obtained from a standardized interview questionnaire. Medical histories of the mother and child were verified through hospital records. Parents were queried about their infant's usual frequency of bowel movements (BMs) before onset of infant botulism because one of the earliest signs of illness is a decrease in the frequency of BMs.[1,22,34,35] Types of food and frequency of feeding were queried in detail for the estimated 3- to 30-day incubation period.[22]

Information collected included parents' and infant's demographics, mother's health, infant's health, infant's feeding history, travel, and the environment in and around the home (**Table I**; available at www.jpeds.com).

Statistical Analyses

Sample size calculations determined that between 133 and 186 infants would be needed in the case and control groups to detect statistically significant differences of 15% in the prevalence of a risk factor with $\alpha = .05$ and $\beta = .20$. Age-at-onset was dichotomized as ≤2 months and >2 months because during the study years infants were often introduced to formula milk or solid foods at about 2-3 months of age.

Bivariate and multivariate analyses were performed for the neighborhood and county controls. All variables with *P* values ≤.05 in the bivariate analyses were evaluated in the multivariate analysis and checked for possible interactions. When an interaction occurs, the effect of one variable in the interaction depends on the level of the other variable in the interaction.

In the multivariate analysis infant feeding experience (other than type of milk) during the incubation period was analyzed using 3 dichotomous variables: consumption of any cereal or sterile solids (eg, commercial jarred baby foods), consumption of any sweeteners (honey, corn syrup, and all other), and consumption of any sterile or non-sterile liquids. Gardening by parents was excluded from the multivariate analysis because it was contained in the variable "any dust exposure." Nested models were compared using the likelihood ratio test. For non-nested models, the lowest value of Akaike's Information Criterion was used to select the best-fitting model.[36] ORs were computed using conditional logistic regression analysis in SAS version 9.4 (SAS Institute Inc, Cary, North Carolina). Tests were considered significant if the 95% CI did not include 1.

Results

A total of 159 cases of infant botulism and 318 controls (184 neighborhood controls and 134 county controls) were included in the analysis; 52% were male. Case race and ethnicity were white (75.5%), Asian (5.0%), other races (2.5%), and black (0.6%); 16% of cases were Hispanic. Ninety-eight (62%) of cases were caused by *C botulinum* type A and 61 (38%) by *C botulinum* type B (including bivalent types Ba and Bf), and none were type F. Mean age at onset was 13.5 ± 0.6 weeks (median: 12.7 weeks; IQR: 10.3 weeks) and differed significantly by toxin type. Mean age at onset for type A cases was 15.5 ± 0.8 weeks (median: 14.1 weeks; IQR: 11.8 weeks) and for type B cases was 10.4 ± 0.8 weeks (median: 9.3 weeks; IQR: 7.4 weeks) (Mann–Whitney *U*, $P < .001$).

The mean difference in age (in days from date of birth) for cases and controls was 4.5 days (median: 2 days; IQR: 7 days). The median distance between case residences and their neighborhood controls was 1.5 km (IQR: 1.8 km) and their county controls was 19.7 km (IQR: 22.3 km). Eight (7.6%) neighborhood controls in sparsely populated counties lived >8 km (>5 miles) away from their associated case. Figure 2 (available at www.jpeds.com) shows the location of cases by county.

A greater percentage of cases was breastfed at illness onset compared with their age-matched controls (Figure 3). Case infants also had a lower BM frequency at illness onset than age-matched control infants (Figure 4). Lower frequency of BMs in case infants compared with age-matched control infants was seen both in the ≤2-month-old and in the >2-month-old age groups (Figure 4).

Bivariate Analyses

No Age Stratification. Risk factors associated with illness hospitalization for all cases compared with their combined neighborhood and county controls with no age stratification are shown in Table II (available at www.jpeds.com). Risk factors associated with illness hospitalization for both neighborhood and county control groups consisted of ≤1 BMs per day, breastfeeding at onset, number of breastfeeds/day, consistent feeding of cereal, sterile solids, and non-sterile liquids anytime since birth and during the incubation period, maternal smoking during pregnancy (OR <1), home in a windy location, excessive dust exposure, and paternal education greater than high school.

Risk factors associated with illness hospitalization for all cases compared with their neighborhood controls consisted

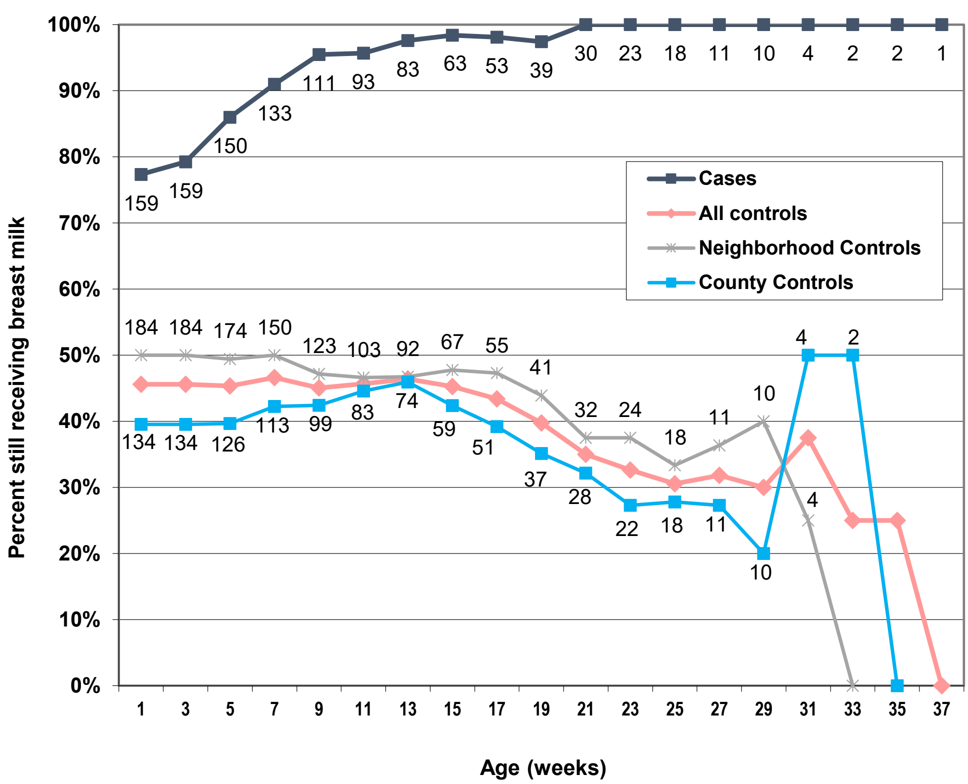
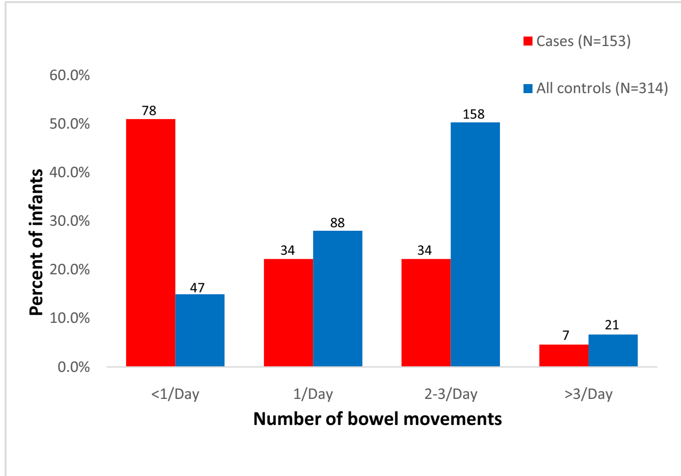
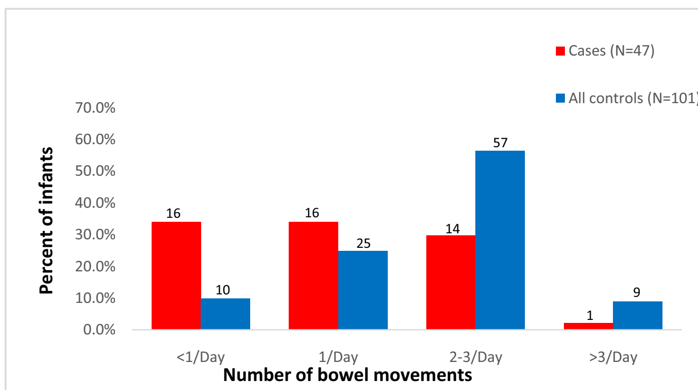


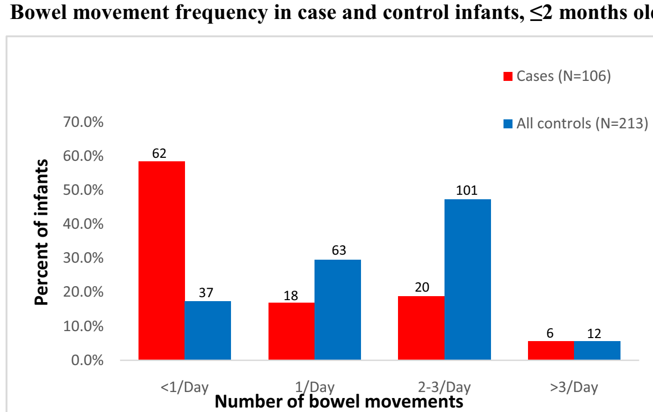
Figure 3. Percentages of case- and age-matched control infants still receiving breast milk by case age-at-onset of infant botulism. *Numbers* at data points are the denominators of cases and controls who remained after younger cases had onset of illness. These denominators were then used to calculate the percentages plotted in the figure.



Bowel movement frequency in all case and control infants



Bowel movement frequency in case and control infants, ≤2 months old



Bowel movement frequency in case and control infants, >2 months old

Figure 4. BM frequency in case and control infants, statified by age. *Integer* denotes the number of case or control infants in the *bar*. Frequency of case BM was before onset of illness, which often manifests as constipation (see Methods). Note that although ≤1 BMs per day was a significant risk factor for infant botulism hospitalization, just 73% of cases had this slower defecation frequency.

of birth order >1, consistent use of honey during any 4-week period between birth and illness onset, first-time use of sweeteners during incubation period, and having moved residence since birth. Respiratory infections since birth and consistent use of corn syrup either for the first time during the incubation period or anytime during a 4-week period between birth and illness onset were factors inversely associated with illness hospitalization (ie, a lower risk for illness hospitalization) (Table II).

Risk factors associated with illness hospitalization for all cases compared just with their county controls consisted of pacifier use, jaundice at birth, partial or exclusive breastfeeding since birth, gardening by parents, trips to non-rural areas before illness, living in a house vs other type of dwelling at illness onset and, for the 4-weeks before onset, older maternal age, higher maternal and paternal education, and race other than white. Having diarrhea or vomiting, not receiving any breast milk, consumption of any non-sterile liquids during the incubation period, and having Hispanic ethnicity were factors that were inversely associated with illness hospitalization (Table II).

Age-Stratified Bivariate Analysis: Cases and Controls ≤2 Months Old. Risk factors associated with illness hospitalization for cases ≤2 months old compared with their neighborhood controls were ≤1 BM per day, pacifier use, feeding non-sterile solids, windy residence location, cesarean delivery, and birth order >1. Feeding corn syrup consistently during the incubation period was inversely related with illness hospitalization (Table III; available at www.jpeds.com).

Risk factors associated with illness hospitalization for cases ≤2 months old compared with their county controls were ≤1 BM per day, pacifier use, receiving breast milk at illness onset, and maternal education greater than high school. Maternal smoking during pregnancy was inversely related with illness hospitalization for cases ≤2 months old compared with their county controls (Table III).

Age-Stratified Bivariate Analysis: Cases and Controls >2 Months Old. Risk factors associated with illness hospitalization for cases compared with their neighborhood controls aged >2 months were ≤1 BM per day, breastfeeding at onset, feeding dextrose water anytime since birth, feeding corn syrup during the incubation period, having parents who gardened, having dust exposure, having moved since birth, birth order >1, and paternal education greater than high school. Risk factors inversely associated with illness hospitalization for cases compared with neighborhood controls aged >2 months were respiratory infections since birth, formula feeding, feeding of most types of sterile or non-sterile solids and liquids, having an air conditioner, and cesarean delivery (Table III).

Risk factors associated with illness hospitalization for cases compared with county controls aged >2 months included ≤1 BM per day, feeding of cereal, sterile solids, non-sterile liquids or sweeteners, windy residence location, having parents who gardened, having any dust exposure, paternal and maternal education greater than high school, and second trimester entry into prenatal care (vs first trimester) (Table III). Consumption of any type of food or beverage other than breast milk or dextrose water was inversely associated with illness hospitalization, as was maternal smoking during pregnancy.

Table IV. Factors significantly associated with California hospitalized patients with infant botulism identified by multivariate analysis with no age-at-onset stratification*

Factors	Versus neighborhood controls (184 controls) aOR† (95% CI)	Versus county controls (134 controls) aOR† (95% CI)
Mother's education		
≤High school‡	1.0	1.0
>High school	2.9 (1.4-6.0)	2.6 (1.2-5.5)
Birth order		
1‡	1.0	
>1	2.7 (1.5-4.8)	NS
Breastfeeding at onset		
No‡		1.0
Yes	NS	7.7 (3.2-18.6)
No. of BMs/d		
>1‡		1.0
≤1	See below	3.5 (1.7-7.1)
Any cereal/sterile solids during incubation period§		
No‡		
Yes	See below	NS
Interaction of cereal/sterile solids and no. BMs/d	See below	NS
>1 BM/d and not fed cereal/sterile solids during incubation period‡	1.0	
>1 BM/d and fed cereal/sterile solids during incubation period	0.3 (0.1-0.6)	
≤1 BM/d and not fed cereal/sterile solids during incubation period	3.3 (1.4-7.6)	
≤1 BM/d and fed cereal/sterile solids during incubation period	4.7 (1.7-12.7)	

*Cases matched with controls on date of birth, sex, ethnicity, and neighborhood of residence (neighborhood controls). Cases matched with controls only on date of birth, sex, and county of residence (county controls).
†Adjusted for the other variables displayed in the table. Variables were considered statistically significant with $P < .05$.
‡Referent group.
§Considered to be 3-30 days.[22]

Information on 144 factors not significantly associated with illness hospitalization may be found in Table I.

Multivariate Analysis

Most risk factors identified in bivariate analysis were found not to be significant in the multivariate analysis. In the multivariate analyses, risk factors significantly associated with illness hospitalization differed by type of control (neighborhood vs county) and age at illness onset (Tables IV-VI). The numbers of case and control infants for each risk factor found to be associated with illness hospitalization in the multivariate analysis, both with and without age stratification, are located in Tables VII-IX.

For neighborhood controls without age stratification, risk factors associated with illness hospitalization were birth order >1 (OR 2.7, 95% CI 1.5-4.8), maternal education greater

Table V. Factors significantly associated with California hospitalized patients with infant botulism identified by multivariate analysis, stratified by age-at-onset*

	Age 0-2 months	
	Versus neighborhood controls (51 cases, 65 controls)	Versus county controls (37 cases, 37 controls)
Factors	aOR† (95% CI)	aOR† (95% CI)
Delivery type		
Vaginal‡	1.0	
Cesarean	5.8 (1.3-26.0)	NS
Birth order		
1‡	1.0	
>1	4.2 (1.3-14.0)	NS
Breastfeeding at onset		
No‡	1.0	
Yes	NS	NS
No. of BMs/d		
>1‡	1.0	
≤1	9.1 (1.6-51.0)	NS
Any cereal/sterile solids during incubation period§		
No‡	1.0	
Yes	NS	NS
Pacifier use		
No‡	1.0	1.0
Yes	NS	7.2 (1.4-36.0)
Resides in windy area		
No‡	1.0	
Yes	3.5 (1.01-12.0)	NS
Dust exposure¶		
No‡	1.0	
Yes	NS	NS
Pets in the home		
No‡	1.0	
Yes	NS	NS

*Cases matched with controls on date of birth, sex, ethnicity, and neighborhood of residence (neighborhood controls). Cases matched with controls only on date of birth, sex, and county of residence (county controls).
†Adjusted for the other variables displayed in the table. Variables were considered statistically significant with $P < .05$.
‡Referent group.
§Considered to be 3-30 days.[22]
¶Any activity in the home or neighborhood following birth that would markedly increase dust or soil exposure (eg, construction, farming, street work, landscaping, ditch digging), or gardening by parents, or maternal/paternal occupational contact with soil.

than high school (OR 2.9, 95% CI 1.4-6.0), and an interaction term of having consumed solids during the incubation period and having ≤1 BM per day (OR 4.7, 95% CI 1.7-12.7) (Table IV).

For neighborhood controls with age stratification, risk factors associated with illness hospitalization for cases aged ≤2 months consisted of birth order >1, cesarean delivery, ≤1 BM per day, and residence in a windy area (Table V).

Risk factors positively associated with illness hospitalization for cases aged >2 months were ≤1 BM per day, breastfeeding at onset, and dust exposure in the home. Feeding cereal/sterile solids during the 3- to 30-day incubation period was inversely associated with illness hospitalization. Infrequent BMs was the only common risk factor for cases aged ≤2 months and those aged >2 months (Table V and Table VI).

Table VI. Factors significantly associated with California hospitalized patients with infant botulism identified by multivariate analysis, stratified by age-at-onset*

	Age >2 months	
	Versus neighborhood controls (108 cases, 119 controls)	Versus county controls (97 cases, 97 controls)
Factors	aOR† (95% CI)	aOR† (95% CI)
Delivery type		
Vaginal‡		
Cesarean	NS	NS
Birth order		
1‡		
>1	NS	NS
Breastfeeding at onset		
No‡	1.0	1.0
Yes	3.8 (1.5-9.8)	11.1 (2.5-48)
No. of BMs/d		
>1‡	1.0	1.0
≤1	3.7 (1.5-9.2)	7.7 (2.3-25)
Any cereal/sterile solids during incubation period§		
No‡	1.0	1.0
Yes	0.3 (0.2-0.8)	0.2 (0.05-0.7)
Pacifier use		
No‡		
Yes	NS	NS
Resides in windy area		
No‡		
Yes	NS	NS
Dust exposure¶		
No‡	1.0	1.0
Yes	3.9 (1.5-10)	4.6 (1.1-19)
Pets in the home		
No‡		1.0
Yes	NS	3.7 (1.1-12)

*Cases matched with controls on date of birth, sex, ethnicity, and neighborhood of residence (neighborhood controls). Cases matched with controls only on date of birth, sex, and county of residence (county controls).
†Adjusted for the other variables displayed in the table. Variables were considered statistically significant with $P < .05$.
‡Referent group.
§Considered to be 3-30 days.[22]
¶Any activity in the home or neighborhood following birth that would markedly increase dust or soil exposure (eg, construction, farming, street work, landscaping, ditch digging), or gardening by parents, or maternal/paternal occupational contact with soil.

For county controls without age stratification, risk factors associated with illness hospitalization were breastfeeding at onset (OR 7.7, 95% CI 3.2-18.6), ≤1 BM per day (OR 3.5, 95% CI 1.7-7.1), and maternal education greater than high school (OR 2.6, 95% CI 1.2-5.5) (Table IV). For county controls with age stratification, the only risk factor identified for cases aged ≤2 months associated with illness hospitalization was pacifier use (OR 7.2, 95% CI 1.4-36) (Table V). Risk factors for cases aged >2 months were breastfeeding at onset, ≤1 BM per day, dust exposure in the home, and pets in the home. Feeding cereal/sterile solids during the incubation period was inversely associated with illness hospitalization (Table VI, Figure 3 and Figure 4).

Table VII. Numbers of case and control infants for factors significantly associated with California hospitalized patients with infant botulism identified by multivariate analysis* with no age-at-onset stratification†

Factors	Versus neighborhood controls (159 cases, 184 controls) Cases (n)	Controls (n)	Versus county controls (134 cases, 134 controls) Cases (n)	Controls (n)
Mother's education				
≤High school‡	65	92	50	84
>High school	94	90	84	50
Unknown§	0	2	0	0
Birth order				
1‡	58	101	52	65
>1	101	83	82	69
Breastfeeding at onset				
No‡	36	92	26	81
Yes	123	92	108	53
No. BMs/d				
>1‡	75	156	63	111
≤1	84	28	71	23
Any cereal/sterile solids during incubation period¶				
No‡	108	84	97	63
Yes	51	100	37	71
Interaction of cereal/sterile solids and no. BMs/d				
>1 BM/d and not fed cereal/sterile solids during incubation period‡	49	66	41	51
>1 BM/d and fed cereal/sterile solids during incubation period	26	90	22	60
≤1 BM/d and not fed cereal/sterile solids during incubation period	59	18	56	12
≤1 BM/d and fed cereal/sterile solids during incubation period.	25	10	15	11

*Adjusted for the other variables displayed in the table. Variables were considered statistically significant with $P < .05$. Only factors found to be significant in the no age-stratified analysis are included in this table.
†Cases matched with controls on date of birth, sex, ethnicity, and neighborhood of residence (neighborhood controls). Cases matched with controls only on date of birth, sex, and county of residence (county controls).
‡Referent group.
§Not included in multivariate analysis.
¶Considered to be 3-30 days.[22]

Table VIII. Numbers of case and control infants for factors significantly associated with California hospitalized patients with infant botulism identified by multivariate analysis,* stratified by age-at-onset†

	Age 0-2 months			
	Versus neighborhood controls (51 cases, 65 controls)		Versus county controls (37 cases, 37 controls)	
Factors	Cases (n)	Controls (n)	Cases (n)	Controls (n)
Delivery type				
Vaginal‡	36	57	25	28
Cesarean	15	8	12	9
Birth order				
1‡	18	39	14	18
>1	33	26	23	19
Breastfeeding at onset				
No‡	25	31	18	26
Yes	26	34	19	11
No. of BMs/d				
>1‡	31	58	24	33
≤1	20	7	13	4
Any cereal/sterile solids during incubation period§				
No‡	31	43	26	22
Yes	20	22	11	15
Pacifier use				
No‡	13	30	7	23
Yes	38	35	30	14
Resides in windy area				
No‡	21	47	17	28
Yes	27	17	17	9
Unknown	3	1	3	0
Dust exposure¶				
No‡	21	29	14	16
Yes	30	36	23	21
Pets in the home				
No‡	31	34	22	19
Yes	20	31	15	18
Unknown	0	0	0	0

*Adjusted for the other variables displayed in the table. Variables were considered statistically significant with $P < .05$. Only factors found to be significant in the no age-stratified analysis are included in this table.
†Cases matched with controls on date of birth, sex, ethnicity, and neighborhood of residence (neighborhood controls). Cases matched with controls only on date of birth, sex, and county of residence (county controls).
‡Referent group.
§Considered to be 3-30 days.[22]
¶Any activity in the home or neighborhood following birth that would markedly increase dust or soil exposure (eg, construction, farming, street work, landscaping, ditch digging), or gardening by parents, or maternal/paternal occupational contact with soil.

Discussion

When this investigation began more than 40 years ago after the first recognition of infant botulism as a novel infectious disease, no information existed about factors that might predispose to, or protect against, acquisition of illness. To remedy this absence, we designed the investigation to enable comprehensive evaluation of prenatal, perinatal, and postpartum aspects of infancy that might predispose to, or protect from, illness. More than 300 potential risk factors were queried by trained interviewers using a standardized questionnaire that encompassed parental demographics, infant health, infant feeding practices, travel, and the home and surrounding environment. Data collection ended in 1983 when federal grant funding ended. Data analysis and reporting were delayed by the approximately 15 years needed to develop and license the public service orphan drug Human Botulism Immune Globulin for infant botulism.[19-21]

A few risk factors of the approximately 300 queried were found to be associated with the illness (Table I contains the listing of the 144 factors queried that were not significantly associated with illness hospitalization.) Several risk factors differed between the ≤2-month-old and >2-month-old age groups, possibly because stratification by age inevitably resulted in loss of statistical power.

This study included all patients hospitalized in California between 1976 and 1983 (1979 excepted; see Methods) with laboratory-confirmed infant botulism (n = 159) and is the largest case-control (n = 318) study of this illness done to date. The study population was stratified into ≤2-month-old and >2-month-old age groups because during the study years, non-milk foods were often introduced into infants' diet at about 2 months of age. Two control infants were

Table IX. Numbers of case and control infants for factors significantly associated with California hospitalized patients with infant botulism identified by multivariate analysis,* stratified by age-at-onset†

	Age >2 months			
	Versus neighborhood controls (108 cases, 119 controls)		Versus county controls (97 cases, 97 controls)	
Factors	Cases (n)	Controls (n)	Cases (n)	Controls (n)
Delivery type				
Vaginal‡	99	92	88	80
Cesarean	9	27	9	17
Birth order				
1‡	40	62	38	47
>1	68	57	59	50
Breastfeeding at onset				
No‡	11	61	8	55
Yes	97	58	89	42
No. of BMs/d				
>1‡	44	98	39	78
≤1	64	21	58	19
Any cereal/sterile solids during incubation period§				
No‡	77	41	71	41
Yes	31	78	26	56
Pacifier use				
No‡	46	48	41	50
Yes	62	71	56	47
Resides in windy area				
No‡	43	61	37	60
Yes	59	57	54	37
Unknown	6	1	6	0
Dust exposure¶				
No‡	16	38	15	35
Yes	92	81	82	62
Pets in the home				
No‡	29	46	26	44
Yes	78	73	70	53
Unknown	1	0	1	0

*Adjusted for the other variables displayed in the table. Variables were considered statistically significant with $P < .05$. Only factors found to be significant in the no age-stratified analysis are included in this table.
†Cases matched with controls on date of birth, sex, ethnicity, and neighborhood of residence (neighborhood controls). Cases matched with controls only on date of birth, sex, and county of residence (county controls).
‡Referent group.
§Considered to be 3-30 days.[22]
¶Any activity in the home or neighborhood following birth that would markedly increase dust or soil exposure (eg, construction, farming, street work, landscaping, ditch digging), or gardening by parents, or maternal/paternal occupational contact with soil.

matched to each case, one termed the "neighborhood control" and the other the "county of residence control." By matching on race and nearby residence, the neighborhood control unintentionally became matched on socioeconomic status. For this reason, after the first 25 patients and 50 controls the matching criteria for the second control were changed to county of residence and no race match.

The only risk factor common to both age groups of patients was having ≤1 BM per day (identified in the ≤2-month-old age group in the neighborhood controls comparison only). Depending on the comparison control group used, ORs associated with having ≤1 BM per day ranged from 3.7-9.1 (Tables IV-VI). These findings extend those of Spika et al, who identified having <1 BM/day for at least 2 months before onset of infant botulism as a risk factor for illness acquisition in infants >2 months of age.[35]

For the younger patients compared with their neighborhood controls (Tables IV-VI), risk factors for infant botulism consisted of cesarean delivery (OR 5.8, 95% CI 1.3-26.0), birth order >1 (OR 4.2, 95% CI 1.3-14.0), having ≤1 BMs per day (OR 9.1, 95% CI 1.6-51.0), and residence in a windy area (OR 3.5, 95% CI 1.01-12.0). For the younger patients compared with their county controls, pacifier use (OR 7.2, 95% CI 1.4-36.0) was the only factor associated with illness hospitalization. As explained subsequently, the paucity of risk factors identified in this stratification was likely the consequence of the small numbers of cases and controls in each group (Table VII).

For the >2-month-old patients, with the exception of pets in the home, risk factors did not differ between the 2 control group comparisons (Tables V and VI). Risk factors for infant botulism for the >2-month-old patients consisted of breastfeeding at onset, having ≤1 BM per day, dust exposure in the home, and feeding cereal/sterile solids during incubation period (inversely associated with illness).

Our interpretation of risk factors identified in this study derives from the ecology of *C botulinum*, a soil-dwelling and dust-borne obligately anaerobic bacterium, and the pathophysiology of infant botulism. In infant botulism swallowed spores of *C botulinum* (or other neurotoxigenic clostridia) germinate in the infant's colon and become vegetative cells that temporarily colonize the colonic microbiome and produce BoNT within it. We suspect that ≤1 BMs per day, ie, a slow intestinal transit time, facilitates germination and outgrowth of swallowed spores.

The composition of the infant's intestinal microbiome in the first 2 months of life is particularly influenced by method of delivery and by diet.[38-40] Comparison of ≤2-month-old cases with their neighborhood controls identified delivery by cesarean delivery as a risk factor for illness, presumably because of resultant differences between the intestinal microbiomes of the case and control infants.[41-43] A possible explanation for birth order >1 being a risk factor in this age group is that breastfeeding a newborn may become more difficult to sustain the more children a mother has. Use of a pacifier by ≤2-month-old cases identified as a risk factor by comparison with county controls suggests possible mechanical conveyance of environmental spores to infants or socioeconomic differences in infant rearing practices between the case and control populations.

The risk factors for infants aged >2 months identified by multivariate analysis were strikingly similar for both the neighborhood and county control groups. For the >2-month-old patients, the risk factors of still being breastfed at illness onset and, inversely, having been fed cereal/sterile solids during the incubation period, again suggest the importance of diet in determining the composition of the intestinal microbiome. Dust exposure as an identified risk factor in the older patients provides an epidemiological counterpart to the identification of *C botulinum* in vacuum cleaner contents from patient homes, in which the toxin type of spores in the vacuum cleaner dust (A or B) always matched the toxin type of the patient's illness (A or B).[44,45] Parenthetically, distribution of *C. botulinum* spores in Californian soils is not uniform[46,47] and may contribute to the observed variation in case occurrence.[48]

This study had limitations. First, it lacked sufficient sample size to detect significant differences for risk factors that were not highly prevalent. To illustrate, after stratification into the 2 age cohorts, 159 infants would have been needed in the comparison group to detect a significant difference for a risk factor with a prevalence of 15% in the cases and 5% in the control group (and vice versa). However, the ≤2-month-old county control group consisted of just 37 case infants and 37 control infants, and significant risk factors in this stratum would have been detected only if they differed by ∼30% or had an OR ≥1.9. Second, data collection relied on accuracy of parental recall. Third, control infants whose parents agreed to participate in the study may have differed from the case infants in unknown ways. Finally, because initial contact was by telephone, families without telephones and therefore likely of lowest socioeconomic status were not represented.

Unlike other studies,[35] controls were selected from the birth population. Interviews were conducted in person, thereby enhancing interview quality and enabling accurate recording of residence and neighborhood characteristics. Comprehensive data were collected about infant feeding practices and maternal and infant health histories (**Table I**).

Two other case–control studies of infant botulism have been published.[35,37] (Another study compared descriptive case information to population norms for just the three characteristics of birthweight, maternal age and parental education.[49]) All 3 case–control studies were done within the first 15 years that followed recognition of this novel infectious disease in 1976.

The study by Long and this study complement each other because of their different designs, different definitions used for important variables, and different geographies. The findings from Spika et al might have contributed additional insight to understanding risk factors for infant botulism, but interpretation is confounded by possible data errors (eg, Table 2, Multivariate Logistic Regression Analysis of Selected Risk Factors, appears to report more breastfed cases in each of its 3 models than there were total cases in each of the 3 models).[35]

The Long study comprised 43 hospitalized cases and 171 control infants who resided in four suburban counties that formed a "ring" around the city and county of Philadelphia and a 44th hospitalized case that resided just inside the Philadelphia county line. Four controls for each case were matched on hospital of birth and date of birth (ie, age). These 5 counties occupy 2202 square miles.[37]

In contrast, this study used 2 controls for each case. The neighborhood control was matched for date of birth (ie, age), sex, race/ethnicity, and neighborhood of residence (±3.2 km; 2.0 mi), and the county control was matched for date of birth, sex, and county of residence. Breaking the de facto socioeconomic match that resulted from matching on race/ethnicity and neighborhood of residence was done to enable evaluation of a possible role of milk feeding (breast vs formula) in illness acquisition. This study consisted of 159 cases and 318 controls who lived throughout California, a state of land area 163 696 square miles (**Figure 2**).

The Long study identified white race, a 2-parent family, having hospital insurance, and being breastfed as risk factors for infant botulism. Major findings of our study identified by multivariate analysis differed between the age-stratified cases and their neighborhood control and county control groups. A slow intestinal transit time (≤1 BMs per day) and dust exposures (including possibly via wind, pacifiers and pets) appear to be important predisposing factors regardless of age, while still being breastfed was predisposing only in the >2-month-old cases.

More than 40 years have passed since first recognition of infant botulism as a novel infectious ("intestinal toxemia") disease in 1976 in California. Since then, infant botulism has been recognized nationwide and worldwide, a treatment has been developed, and its descriptive epidemiology has been studied in many locations.[20,34-35,37,49-54] However, the Long case–control study and this case–control study both finished patient enrollment more than 35 years ago. The time may be ripe for new case–control studies to ascertain risk factors for infant botulism in the 21st century. ■

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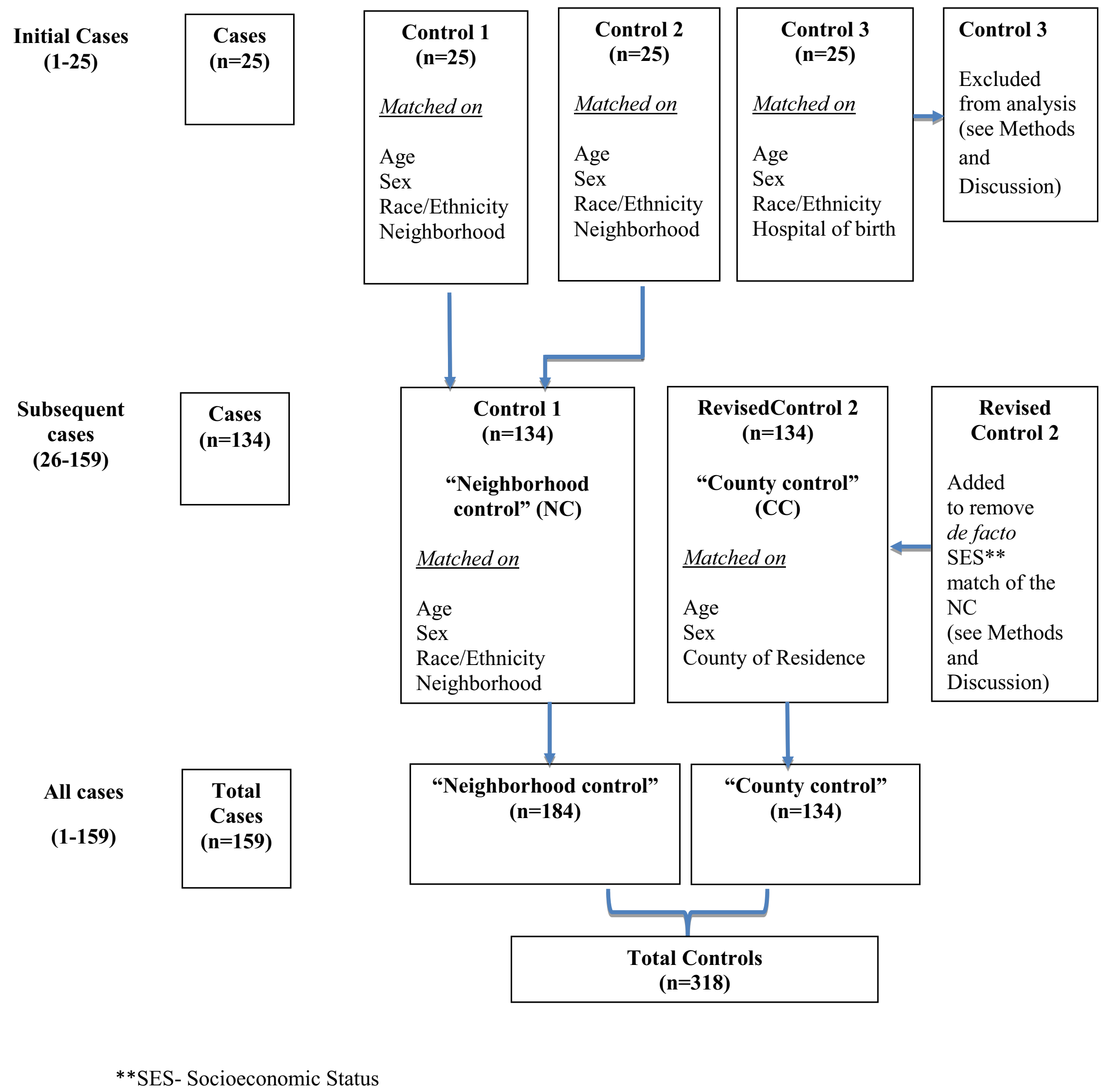

Figure 1. Flow chart displaying selection of study cases and controls.

County	No. of cases
Alameda	7
Amador	1
Butte	2
Contra Costa	5
El Dorado	3
Fresno	2
Kern	5
Los Angeles	48
Madera	1
Merced	1
Monterey	9
Napa	1
Orange	7
Placer	2
Riverside	2
Sacramento	7
San Benito	1
San Bernardino	7
San Diego	7
San Francisco	4
San Joaquin	2
San Luis Obispo	4
San Mateo	2
Santa Barbara	3
Santa Clara	11
Santa Cruz	2
Sonoma	3
Stanislaus	2
Ventura	5
Washoe, Nevada*	2
Yolo	1
Total Cases	**159**
*Hospitalized in CA	

Figure 2. Case residence by county in the California infant botulism case–control study, 1976-1983.

Table I. Factors not significantly associated[*] with hospitalization from infant botulism in California identified by comparison with neighborhood and county control groups using bivariate analysis and no age stratification

Factors	Case infants (n = 159) n (%)	Neighborhood controls (n = 184) n (%)	Unadjusted OR (95% CI)	Case infants (n = 134) n (%)	County controls (n = 134) n (%)	Unadjusted OR (95% CI)
Parental variables						
When prenatal care began						
(categorized as first trimester [referent], second trimester, third trimester, no prenatal care)			NS[†]			NS
Parturition			NS			NS
(vaginal vs cesarean delivery; singleton vs twin)			NS			NS
Maternal blood group						
(categorized as A, B, AB, O [referent]; Rh+ vs Rh–)			NS			NS
Maternal education						
(stratified into categories of <high school [referent], high school, some college, college degree, advanced degree; and ≥high school vs <high school)			NS			NS
Paternal age						
(stratified into 5-y age intervals from 15 to 49, referent: 15-19)			NS	‡	‡	‡
Paternal education						
(stratified into categories of <high school [referent], high school, some college, college degree, advanced degree; and >high school vs ≤high school)			NS			NS
≥high school vs <high school			NS	‡	‡	‡
Infant demographics						
Infant's ethnicity						
(categorized as Asian, black, Hispanic, Native American, white [referent], other)			NA - matched	‡	‡	‡
Infant birth characteristics						
(birth weight <2500 g vs ≥2500 g; premature [<37 wk] vs ≥37 wk; gestational age >42 wk vs ≤42 wk)			NS			NS
Birth order >1 vs 1	‡	‡	‡			NS
Ever use of pacifier vs not			NS	‡	‡	‡
Infant health						
(Antibiotic use >1 mo before onset; antibiotic use <1 mo of onset; any immunizations[§] since birth)			NS			NS
Illness since birth vs not						
(Thrush; ear infections; eye infections; wound infections; colic; any illness)			NS			NS
Respiratory infections	‡	‡	‡			NS
Jaundice			NS	‡	‡	‡
Diarrhea and vomiting			NS	‡	‡	‡
Infant nutrition history						
Breastfeeding since birth						
Exclusive FF	21 (13)	42 (23)	1.0	‡	‡	‡
Partial BF	108 (68)	117 (64)	1.9 (0.99-3.5)[¶]			
Exclusive BF	30 (19)	25 (14)	2.2 (0.99-4.9)[¶]			
Milk feeding type						
(categorized as only breast milk [referent], liquid formula, powder formula, liquid and powder)			NS	‡	‡	‡
Breast milk expression						
(categorized as none expressed [referent], expressed for future, no BF)			NS	‡	‡	‡
Any tastes since birth vs not						
(cereal; non-sterile solids; non-sterile liquids; sterile liquids; honey; corn syrup; sweeteners[¶])			NS			NS
Any use in any 4-wk period between birth and onset vs not						

(*continued*)

Table I. Continued

Factors	Case infants (n = 159) n (%)	Neighborhood controls (n = 184) n (%)	Unadjusted OR (95% CI)	Case infants (n = 134) n (%)	County controls (n = 134) n (%)	Unadjusted OR (95% CI)
(non-sterile solids; non-sterile liquids; sterile liquids; honey; corn syrup; sweeteners¶)			NS			NS
Consistent use (≥3) within any 4-wk period between birth and onset vs not						
(non-sterile solids; sterile liquids; corn syrup; sweeteners**; 5% dextrose water)			NS			NS
Honey	‡	‡	‡			NS
Corn syrup	‡	‡	‡			NS
Any use during incubation period†† vs not						
(Non-sterile solids; sterile liquids; corn syrup; sweeteners**; 5% dextrose water)			NS			NS
Consistent use during incubation period†† vs not						
(non-sterile solids; sterile liquids; honey; corn syrup; sweeteners*; 5% dextrose water)			NS			NS
First-time use during incubation period†† vs not						
(cereal, non-sterile solids; sterile solids; non-sterile liquids; sterile liquids; honey; corn syrup; 5% dextrose water)			NS			NS
Sweeteners**	‡	‡	‡			NS
First-time consistent use during incubation period†† vs not						
(cereal; non-sterile solids; non-sterile liquids; sterile liquids; honey; sweeteners**; 5% dextrose water)			NS			NS
Corn syrup	‡	‡	‡			NS
Vitamin use						
(Any use vs none; use <4 wk of onset)			NS			NS
Infant's environment						
(Pets at home; plants at home; air conditioning; rural residence vs urban/suburban 4 wk before onset; trips to rural area‡‡ before onset)			NS			NS
Moved since birth vs not	‡	‡	‡			NS
Rural residence at onset vs urban/suburban	31 (19)	21 (11)	3.0 (0.99-9.4)¶			NS
Trips to non-rural‡‡ area before onset vs not			NS	‡	‡	‡
Parents gardening vs not			NS	‡	‡	‡
Lived in house at onset vs apartment, condo, trailer, duplex or other			NS	‡	‡	‡
Lived in house 4 wk before onset vs apartment, condo, trailer, duplex or other			NS	‡	‡	‡
Hygiene practices						
Hand washing before BF for BF infants			NS			NS
Hand washing before FF for FF infants			NS			NS
Bottle washing						
(categorized as boiled in water/dishwasher [referent], no bottle use [BF], hand washed in soap/water, rinsed/not washed)			NS			NS

BF, breastfed; *DTP*, diphtheria, pertussis, and tetanus; *FF*, formula-fed; *NA*, not available; *NS*, not significant; *OPV*, oral polio vaccine.
*No significant association was defined as a 95% CI for the OR from conditional logistic regression that included 1.0. For categorical variables, if ≥1 category was statistically significant, the data are presented in Table II. Missing responses for each variable were included in the model as an unknown category but are not shown in the table.
†Not significant.
‡See Table II for categories with statistically significant associations.
§First DPT, second DPT, third DPT, first OPV, second OPV, and third OPV. ORs for individual immunization series (DPT or OPV) were also not significant.
¶.05 < P < .06.
**Excluding honey or corn syrup.
††Considered to be 3-30 days.[22]
‡‡Defined as farms, mountains, lakes, deserts, wilderness, and campgrounds.

Table II. Factors significantly associated with California hospitalized patients with infant botulism identified by bivariate comparison with the neighborhood and county control groups with no age-at-onset stratification*

Factors	Versus neighborhood controls (n = 159 cases, n = 184 controls) Unadjusted OR[†] (95% CI)	Versus county controls (n = 134 cases, n = 134 controls) Unadjusted OR[†] (95% CI)
Infant health/pacifier use		
Birth order >1 vs 1	**2.0 (1.3-3.0)**	1.4 (0.9-2.3)
Ever use of pacifier vs not	1.2 (0.8-1.9)	**2.0 (1.2-3.2)**
History of ≤1 BM/d vs >1 BM/d	**6.0 (3.3-10.9)**	**4.4 (2.5-7.9)**
Respiratory infections vs not	**0.4 (0.2-0.8)**	0.6 (0.4-1.1)
Diarrhea and vomiting vs not	0.8 (0.5-1.3)	**0.5 (0.3-0.9)**
Jaundice vs not	0.9 (0.6-1.5)	**1.8 (1.03-3.3)**
Infant nutrition history		
Breastfeeding since birth		
Exclusive FF[‡]	1.0	1.0
Partial BF	1.9 (1.0-3.5)	**5.5 (2.3-13.1)**
Exclusive BF	2.2 (1.0-4.9)	**9.0 (3.1-26.3)**
Breastfeeding at onset		
Exclusive FF[‡]	1.0	1.0
Partial BF	**3.1 (1.7-5.5)**	**7.3 (3.2-16.7)**
Exclusive BF	**3.7 (2.0-7.0)**	**10.7 (4.4-26.0)**
No. breastfeeds/d at onset		
≥1 vs none	**2.9 (1.8-4.6)**	**10.3 (4.5-23.9)**
None[‡]	1.0	1.0
<6	**2.4 (1.2-5.0)**	**4.5 (1.7-12.4)**
≥6	**3.0 (1.9-4.9)**	**16.1 (6.0-43.0)**
Breast milk expression		
None expressed[‡]	1.0	1.0
Expressed for future use	1.8 (0.9-3.9)	1.7 (0.9-3.2)
No BF (100% FF)	1.8 (1.0-3.5)	**0.2 (0.1-0.5)**
Any use within any 4-wk period between birth and onset vs not		
Cereal	**0.4 (0.3-0.7)**	**0.3 (0.2-0.6)**
Sterile solids	**0.2 (0.1-0.4)**	**0.2 (0.1-0.4)**
5% dextrose water	**1.7 (1.04-2.8)**	**2.7 (1.5-4.8)**
Consistent use (≥3) within any 4-wk period between birth and onset vs not		
Cereal	**0.3 (0.2-0.5)**	**0.3 (0.1-0.5)**
Sterile solids	**0.1 (0.05-0.3)**	**0.1 (0.04-0.3)**
Non-sterile liquids	**0.5 (0.3-0.9)**	**0.3 (0.2-0.6)**
Honey	**2.6 (1.1-6.4)**	2.0 (0.6-6.6)
Corn syrup	**0.5 (0.3-0.9)**	0.8 (0.02-1.1)
Any use during incubation period[§] vs not		
Cereal	**0.4 (0.3-0.7)**	**0.3 (0.2-0.6)**
Sterile solids	**0.2 (0.1-0.4)**	**0.2 (0.1-0.4)**
Non-sterile liquids	0.8 (0.5-1.2)	**0.6 (0.3-0.9)**
Honey	**2.4 (1.1-5.0)**	**3.8 (1.2-11.3)**
Consistent use during incubation period[§] vs not		
Cereal	**0.3 (0.2-0.5)**	**0.3 (0.1-0.5)**
Sterile solids	**0.1 (0.05-0.3)**	**0.1 (0.05-0.3)**
Non-sterile liquids	**0.4 (0.2-0.7)**	**0.3 (0.1-0.5)**
First-time use during incubation period[§] vs not		
sweeteners	**2.6 (1.1-6.0)**	1.7 (0.7-3.9)
First-time consistent use during incubation period[§] vs not		
Sterile solids	**0.4 (0.1-0.9)**	**0.3 (0.1-0.9)**
Corn syrup	**0.1 (0.03-0.6)**	0.5 (0.1-2.7)
Infant's environment		
Maternal smoking during pregnancy vs none	**0.5 (0.3-0.9)**	**0.3 (0.1-0.6)**
Home in a windy location vs not	**2.0 (1.2-3.1)**	**2.4 (1.4-4.2)**
Any dust exposure[¶] vs not	**1.8 (1.1-2.9)**	**2.5 (1.4-4.5)**
Moved since birth vs not	**2.9 (1.2-6.8)**	1.1 (0.6-2.3)
Parents gardening vs not	1.4 (0.9-2.2)	**2.4 (1.4-4.2)**
Trips to non-rural area prior to illness vs not	0.8 (0.4-1.7)	**2.8 (1.4-5.6)**
Lived in house 4 wk prior to onset vs apartment, condo, trailer, duplex or other	1.4 (0.8-2.4)	**2.3 (1.3-4.1)**
Lived in house at onset vs apartment, condo, trailer, duplex or other	1.3 (0.8-2.3)	**2.4 (1.3-4.3)**
Parental demographics		
Maternal age, y		
15-19[‡]	1.0	1.0
20-24	1.6 (0.6-4.4)	3.0 (0.9-9.5)
25-29	2.1 (0.8-5.7)	**4.2 (1.3-13.4)**
30-34	2.5 (0.8-7.6)	**7.6 (2.2-26.1)**
35-39	**24.5 (4.1-148.0)**	**6.0 (1.5-23.9)**
40-44	10.6 (0.5-208.0)	**13.4 (1.01-171.0)**

(*continued*)

Table II. Continued

Factors	Versus neighborhood controls (n = 159 cases, n = 184 controls)	Versus county controls (n = 134 cases, n = 134 controls)
	Unadjusted OR† (95% CI)	Unadjusted OR† (95% CI)
Maternal education		
<High school‡	1.0	1.0
High school diploma	0.8 (0.4-1.6)	0.9 (0.4-2.2)
Some college	1.6 (0.7-3.3)	**4.6 (1.9-11.4)**
College degree	1.7 (0.7-3.8)	**2.7 (1.02-7.2)**
Advanced degree	0.8 (0.2-2.7)	1.1 (0.3-4.0)
>High school vs ≤high school	1.1 (0.6-2.1)	**4.0 (2.1-7.5)**
Paternal age, y		
15-19‡	1.0	1.0
20-24	0.7 (0.2-3.5)	4.8 (0.5-43.9)
25-29	0.8 (0.2-3.7)	5.8 (0.7-48.1)
30-34	1.2 (0.3-5.9)	7.3 (0.9-61.9)
35-39	2.3 (0.4-12.0)	**13.3 (1.5-121.0)**
40-44	2.6 (0.3-20.4)	7.0 (0.7-73.9)
45-49	2.0 (0.2-21.6)	6.5 (0.2-213.3)
Paternal education		
>High school vs ≤high school	**2.1 (1.2-3.7)**	**2.8 (1.6-4.8)**
Infant's ethnicity		
White vs all other	NA – matched	**2.7 (1.4-5.2)**
White‡	NA – matched	1.0
Asian	NA – matched	0.6 (0.2-2.2)
Black	NA – matched	Undefined**
Hispanic	NA – matched	**0.4 (0.2-0.9)**
Native American	NA – matched	0.4 (0.02-7.4)
Other	NA – matched	0.6 (0.04-11.3)

*See Methods for description of neighborhood and county control groups. Neighborhood controls were matched on case birth date, sex, ethnicity, and neighborhood of residence (≤3.2-km radius of case home). County controls were matched only on case birth date, sex, and county of residence. The OR for both control groups are shown, even if the OR was significant for only one control group. Factors significantly associated with illness are in bold.
†95% CIs were calculated by conditional logistic regression. Missing responses for each variable were included in the model as an unknown category but are not shown in the table.
‡Referent group.
§Considered to be 3-30 days.[22]
¶Any activity in the home or neighborhood since the infant was born that would markedly contribute to an increase in dust/soil/dirt exposure (eg, construction, farming, street work, landscaping, ditch digging), gardening by parents, or maternal/paternal occupational contact with soil.
**At least 1 of the cells contains '0'; hence, OR is undefined.

Table III. Factors significantly associated with California hospitalized patients with infant botulism identified by bivariate comparison with the neighborhood and county control groups, stratified by age-at-onset*

	Age 0-2 months		Age >2 months	
	Versus neighborhood controls (n = 51 cases, n = 65 controls)	Versus county controls (n = 37 cases, n = 37 controls)	Versus neighborhood controls (n = 108 cases, n = 119 controls)	Versus county controls (n = 97 cases, n = 97 controls)
Factors	**Unadjusted OR† (95% CI)**	**Unadjusted OR† (95% CI)**	**Unadjusted OR† (95% CI)**	**Unadjusted OR† (95% CI)**
Infant health/frequency of BM/pacifier use/URIs				
>1 BM/d‡	1.0	1.0	1.0	1.0
≤1 BM/d	**4.5 (1.6-12.2)**	**3.7 (1.02-13.1)**	**6.9 (3.3-14.6)**	**4.5 (2.4-8.7)**
No pacifier use‡	1.0	1.0	1.0	1.0
Pacifier use	**2.5 (1.03-6.1)**	**9.0 (2.1-38.8)**	0.9 (0.5-1.6)	1.3 (0.8-2.3)
No respiratory infections since birth‡	1.0	1.0	1.0	1.0
Respiratory infections since birth	0.9 (0.3-2.7)	1.3 (0.3-4.7)	**0.3 (0.2-0.7)**	**0.6 (0.3-0.9)**
Infant nutrition history				
Breastfeeding				
No breastfeeding at onset‡	1.0	1.0	1.0	1.0
Some breastfeeding at onset	0.9 (0.4-1.8)	**3.7 (1.02-13.1)**	**6.8 (3.2-14.4)**	17.0 (5.3-54.5)
No breast milk expressed for future use‡	1.0	1.0	1.0	1.0
Formula feeding	1.2 (0.4-3.1)	0.4 (0.1-1.2)	**0.2 (0.1-0.7)**	**0.1 (0.02-0.4)**
Breastmilk expressed for future use	**0.3 (0.1-0.9)**	1.5 (0.3-8.7)	1.6 (0.8-2.9)	1.6 (0.8-3.3)
Any tastes between birth and onset				
Non-sterile solids	**3.3 (1.01-11.0)**	3.0 (0.3-28.8)	0.9 (0.4-1.8)	1.4 (0.6-3.4)
Any use within any 4-wk period between birth and onset				
Non-sterile solids	3.8 (1.0-14.4)	5.0 (0.6-42.8)	1.0 (0.6-1.9)	1.6 (0.8-3.1)
Cereal	1.6 (0.6-3.8)	0.5 (0.2-1.7)	**0.2 (0.1-0.5)**	**0.3 (0.1-0.5)**
Sterile solids	2.0 (0.6-6.1)	0.6 (0.1-2.5)	**0.1 (0.01-0.2)**	**0.1 (0.04-0.3)**
Non-sterile liquids	2.0 (0.8-5.3)	0.7 (0.4-1.2)	0.7 (0.2-1.9)	0.6 (0.3-1.2)
Corn syrup	0.9 (0.4-2.0)	0.5 (0.3-1.0)	0.7 (0.3-1.8)	0.6 (0.3-1.2)
5% dextrose water	1.3 (0.5- 3.2)	1.7 (0.4-7.0)	**1.8 (1.01-3.2)**	**3.2 (1.6-6.3)**
Any use during estimated incubation period§				
Non-sterile solids	3.8 (1.0-14.4)	5.0 (0.6-42.8)	1.1 (0.7-1.9)	1.2 (0.7-2.2)
Cereal	1.6 (0.6-3.8)	0.5 (0.2-1.7)	**0.2 (0.1-0.4)**	**0.3 (0.1-0.5)**
Sterile solids	2.2 (0.7-6.7)	0.6 (0.1-2.5)	**0.02 (0.003-0.2)**	**0.1 (0.04-0.3)**
Non-sterile liquids	2.4 (0.9- 6.5)	0.9 (0.3-2.6)	**0.5 (0.3-0.9)**	**0.5 (0.2-0.9)**
Corn syrup	1.7 (0.5-5.5)	0.8 (0.3-2.1)	**2.9 (1.1-7.7)**	1.1 (0.5-2.6)
5% dextrose water	0.8 (0.1-4.6)	1.0 (0.1-16.0)	Undefined¶	Undefined¶
Consistent use (≥3 times) within any 4-wk period between birth and onset				
Non-sterile solids	2.6 (0.2-29.1)	0.7 (0.3-1.6)	Undefined¶	0.7 (0.4-1.4)
Cereal	1.9 (0.7-5.5)	1.0 (0.3-3.5)	**0.2 (0.1-0.3)**	**0.2 (0.1-0.4)**
Sterile solids	0.8 (0.2-3.0)	0.2 (0.02-1.7)	**0.04 (0.01-0.2)**	**0.1 (0.03-0.3)**
Non-sterile liquids	1.7 (0.4-7.5)	0.4 (0.1-1.4)	**0.5 (0.3-0.8)**	**0.3 (0.1-0.6)**
Corn syrup	0.7 (0.3-1.7)	0.8 (0.2-3.0)	**0.4 (0.2-0.9)**	**0.4 (0.2-0.9)**
5% dextrose water	Undefined¶	3.6 (0.9-14.0)	0.7 (0.1-4.3)	1.2 (0.5-2.9)
Consistent use (≥3 times) during incubation period§				
Non-sterile solids	2.6 (0.2-29.1)	0.5 (0.2-1.2)	Undefined¶	0.5 (0.2-1.1)
Cereal	1.9 (0.7-5.5)	1.0 (0.3-3.5)	**0.2 (0.1-0.3)**	**0.2 (0.1-0.4)**
Sterile solids	0.8 (0.2-3.0)	0.4 (0.1-2.1)	**0.04 (0.01-0.2)**	**0.1 (0.03-0.3)**
Non-sterile liquids	2.8 (0.5-15.2)	0.6 (0.2-2.0)	**0.3 (0.2-0.6)**	**0.2 (0.1-0.5)**
Corn syrup	0.5 (0.2-1.5)	0.5 (0.2-1.3)	1.0 (0.3-3.5)	0.9 (0.3-2.4)
5% dextrose water	Undefined¶	1.0 (0.1-16.0)	Undefined¶	Undefined¶
First-time use during incubation period§				
Non-sterile solids	3.8 (1.0-14.4)	5.0 (0.6-42.8)	1.1 (0.6-2.1)	1.5 (0.7-3.3)
Cereal	2.6 (0.9-7.7)	0.5 (0.2-1.2)	0.5 (0.2-1.7)	0.8 (0.4-1.7)
Non-sterile liquids	**3.5 (1.2-9.9)**	0.7 (0.2-2.3)	1.0 (0.5-2.1)	1.9 (0.7-4.6)
Corn syrup	0.5 (0.2-1.4)	0.7 (0.2-2.0)	0.4 (0.1-1.4)	1.3 (0.3-6.0)
5% dextrose water	1.2 (0.2-8.6)	Undefined¶	Undefined¶	Undefined¶
First-time consistent use (≥3 times) during incubation period§				
Non-sterile solids	2.6 (0.2-29.1)	0.7 (0.2-2.1)	Undefined¶	0.7 (0.2-2.3)
Cereal	2.6 (0.9-7.7)	0.5 (0.2-1.2)	1.0 (0.3-3.5)	0.6 (0.2-1.6)

(continued)

Table III. Continued

	Age 0-2 months		Age >2 months	
	Versus neighborhood controls (n = 51 cases, n = 65 controls)	Versus county controls (n = 37 cases, n = 37 controls)	Versus neighborhood controls (n = 108 cases, n = 119 controls)	Versus county controls (n = 97 cases, n = 97 controls)
Factors	Unadjusted OR† (95% CI)	Unadjusted OR† (95% CI)	Unadjusted OR† (95% CI)	Unadjusted OR† (95% CI)
Sterile solids	0.9 (0.3-3.4)	0.5 (0.1-2.7)	**0.2 (0.04-0.7)**	**0.2 (0.04-0.9)**
Corn syrup	**0.1 (0.01-0.8)**	0.3 (0.03-3.2)	0.2 (0.02-1.9)	1.0 (0.06-16.0)
5% dextrose water	0.5 (0.0-4.5)	Undefined¶	Undefined¶	Undefined¶
Infant's environment				
No maternal smoking during pregnancy‡	1.0	1.0	1.0	1.0
Maternal smoking during pregnancy	0.4 (0.2-1.0)	**0.1 (0.01-0.6)**	0.6 (0.3-1.2)	**0.4 (0.2-0.8)**
Home not in a windy location‡	1.0	1.0	1.0	1.0
Home in a windy location	**5.0 (1.8-13.8)**	2.6 (0.9-7.3)	1.4 (0.8-2.4)	**2.4 (1.3-4.6)**
No parents gardening‡	1.0	1.0	1.0	1.0
Parents gardening	0.8 (0.4-1.8)	2.0 (0.8-5.3)	**1.9 (1.1-3.3)**	**2.7 (1.4-5.2)**
No exposure to dust‡,**	1.0	1.0	1.0	1.0
Any exposure to dust	1.1 (0.5-2.4)	1.3 (0.5-3.5)	**2.5 (1.3-4.8)**	**3.5 (1.6-7.7)**
No air conditioning at home‡	1.0	1.0	1.0	1.0
Air conditioning at home	1.6 (0.4-6.6)	0.9 (0.3-2.6)	**0.4 (0.2-0.9)**	1.0 (0.5-2.1)
Never moved residence/home since birth‡	1.0	1.0	1.0	1.0
Moved residence/home since birth	1.3 (0.2-8.0)	1.0 (0.1-7.1)	**3.5 (1.3-9.6)**	1.2 (0.5-2.5)
Birth characteristics				
Mode of delivery				
Vaginal delivery‡	1.0	1.0	1.0	1.0
Cesarean delivery	**3.5 (1.1-10.9)**	1.6 (0.5-4.9)	**0.3 (0.1-0.6)**	0.5 (0.2-1.1)
Birth order				
Birth order 1‡	1.0	1.0	1.0	1.0
Birth order >1	**2.3 (1.1-4.8)**	1.4 (0.6-3.4)	**1.8 (1.1-3.0)**	1.5 (0.8-2.6)
Parental demographics				
Maternal education				
≤High school‡	1.0	1.0	1.0	1.0
>High shcool	1.3 (0.5-3.4)	**4.3 (1.4-12.6)**	1.9 (1.0-3.5)	**2.9 (1.5-5.8)**
Paternal education				
≤High school‡	1.0	1.0	1.0	1.0
>High school	1.9 (0.7-5.3)	2.3 (0.9-5.6)	**2.2 (1.1-4.3)**	**2.8 (1.5-5.5)**
Maternal health				
Entry into prenatal care				
First trimester‡	1.0	1.0	1.0	1.0
Second trimester	1.0 (0.4-2.7)	0.8 (0.3-3.4)	1.5 (0.7-3.1)	**3.3 (1.1-10.0)**
Third trimester	Undefined¶	Undefined¶	Undefined¶	Undefined¶
No prenatal care	Undefined¶	Undefined¶	Undefined¶	Undefined¶

URI, upper respiratory infection.
*See Methods for description of neighborhood and county control groups. Neighborhood controls were matched on case birth date, sex, ethnicity, and neighborhood of residence (≤3.2-km radius of case home). County controls were matched only on case birth date, sex, and county of residence. The ORs for both age categories are shown, even if the OR was significant in only one age category. Factors significantly associated with illness are bolded.
†95% CIs were calculated by conditional logistic regression. Missing responses for each variable were included in the regression model as an unknown category but are not included in the table.
‡Referent group.
§Considered to be 3-30 days.[22]
¶At least one cell contains a "0"; hence, OR is undefined.
**Any activity in the home or neighborhood since the infant was born that would markedly contribute to an increase in dust/soil/dirt exposure (eg, construction, farming, street work, landscaping, ditch digging), gardening by parents, or maternal/paternal occupational contact with soil.