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Invasive Haemophilus influenzae Serotype a Infection in Children: Clinical Description of an Emerging Pathogen — Alaska, 2002–2014

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Abstract

Background—Invasive infections from *Haemophilus influenzae* serotype a (Hia) have been reported with increasing frequency, especially among indigenous populations. However there are limited population-based-studies of clinical severity. We studied invasive Hia infections in Alaska to determine clinical characteristics, mortality, and sequelae.

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Methods—We defined an invasive Hia infection as the first detection of Hia from a usually sterile site in a child <10 years of age from Alaska. We identified cases using the Alaska Invasive Bacterial Diseases Surveillance System and reviewed medical charts up to 2 years after reported illness.

Results—We identified invasive Hia infections in 36 children, 28 (78%) <1 year old, 34 (94%) living in an Alaskan village, and 25 (69%) without documented underlying illness. Overlapping clinical presentations included meningitis in 15 children (42%); bacteremia and pneumonia in 10 children (28%); and bone, joint or soft tissue infections in 10 children (22%). In four other children, no source of invasive infection was identified. Intensive care was provided for 11 children (31%); 12 children (33%) required surgical intervention. One year after infection, 4 children (11%) had died from Hia, and 5 children (14%) had ongoing neurologic sequelae.

Conclusions—Invasive Hia infections in Alaska occurred predominantly in Alaska Native infants in rural communities. Although one-third of children had pre-existing conditions, most cases occurred without known comorbidity. Clinical syndromes were frequently severe. One year after infection, one in four children had either died or had neurologic sequelae. An effective vaccine would prevent significant morbidity and mortality in affected populations.

Keywords

Alaska; H. influenzae; Hia; invasive disease; meningitis

Introduction

Infection with *Haemophilus influenzae* may lead to asymptomatic carriage or clinical disease, including pneumonia, sepsis, and meningitis (1). The capsule of *H. influenzae* contributes to virulence in the 6 described serotypes (a–f), with other strains lacking capsules described as non-typeable (2). *H. influenzae* serotype b (Hib) was the main cause of bacterial meningitis historically in the United States (3), and disproportionately affected indigenous communities (1, 4)—including Alaska Native populations (5), where rates of invasive Hib disease were over 300 per 100,000 in children under 5 years old (6). Following the introduction of conjugate vaccines incidence rates of invasive Hib disease declined over 99%, and have remained low since (6–8).

However in recent years there has been increasing recognition of the emergence of non-b serotypes for which there are no available vaccines, including *H. influenzae* serotype a (Hia) (2, 9, 10). While surveillance systems in Kenya (11), Australia (12), and Europe (13) have detected relatively few cases of invasive Hia disease, an increase in reported cases has been noted in Brazil (14) and North America (9, 15, 16). In some indigenous populations in the United States and Canada, incidence rates of invasive Hia disease >200 per 100,000 in children under 5 years of age have been reported (2, 9, 15) including among Alaska Native populations in southwestern Alaska (9), compared with an overall incidence rate in Alaska of 5.4 per 100,000 in children under 5 years of age (9).

There are several published clinical descriptions of severe Hia infections, including a cluster of linked cases in Southwestern Alaska (17), and descriptions from other regions (2, 18).

Collectively, the evidence suggests that invasive disease with Hia typically affects young children and can cause severe clinical syndromes such as meningitis, pneumonia and septic arthritis. However, only a few studies have reported how representative these cases are, or summarized disease severity at the population level ((15, 16, 18, 19), Table 1). In this study we characterized clinical Hia severity using a population-based surveillance system. To determine the severity of invasive Hia disease in children, we reviewed background characteristics, clinical severity, and outcomes at 1 year, in children identified through statewide bacterial disease surveillance in Alaska.

Materials and Methods

Study design and population

We performed a retrospective chart review of Hia infections identified by the Alaska Invasive Bacterial Diseases Surveillance System between January 2002 and July 2014. This statewide surveillance system has been described elsewhere (9), and provides consistent audited surveillance of invasive bacterial infections through submission of bacterial isolates in Alaska. Clinical laboratories are requested to send all bacterial isolates of included pathogens to the Arctic Investigations Program in Anchorage for further evaluation.

Case definition

We defined a case of invasive Hia as the first detection of Hia from a sterile site by bacterial culture or by PCR, in a child with an acute illness who is aged <10 years and a resident of Alaska. Site of infection was defined as meningitis if Hia was detected in cerebrospinal fluid (CSF) or if Hia was detected from another sterile site and meningitis was evident from lumbar puncture or MRI; as pneumonia if there was a clinical diagnosis; and as other foci such as soft tissue infection according to the clinical diagnosis. We defined underlying illness as any chronic illness at the time of presentation, and sequelae at 1 year as any complication of Hia infection reported at least 1 year after illness resulting in a new loss of function.

Laboratory methods

H. influenzae was confirmed by Gram stain and factor X and V requirements (Differentiation Disks; Difco Laboratories, Detroit, MI). Isolates were serotyped by slide agglutination (*H. influenzae* serotypes a-f typing antisera; Difco). For specimens that were culture negative, serotyping was performed by PCR amplification of serotype-specific genes (20). Antimicrobial susceptibility testing was performed using Etest® strips (bioMérieux, Inc., Durham, NC).

Clinical and outcome data.

We performed chart reviews on all cases using a standard form to describe clinical presentation, management, complications and any sequelae. Optimal duration of antimicrobials were defined as at least 7 days' intravenous therapy for bacteremia or meningitis (21), 21 days for septic arthritis and 42 days for osteomyelitis (22). To identify any reported underlying illness or sequelae, we reviewed charts for 6 months before illness onset, and for up to 2 years after resolution of the initial illness associated with Hia

infection. We assessed vaccination status with Hib vaccine using data routinely collected from laboratories and providers as part of bacterial diseases surveillance. Children in Alaska routinely receive PRP-OMP (PedvaxHIB, Merck and Co., Inc., Whitehouse Station, New Jersey). The primary series of PRP-OMP is 2 doses recommended at 2 and 4 months, followed by a booster dose at age ≥12 months. Children were considered to have age-appropriate Hib vaccination if 1 dose had been given before age 3 months, 2 doses before age 5 months, or 3 doses before age 16 months; or if a catch up schedule was followed, with a 1st dose was given >7 months and a 2nd ≥12 months, or with a 1st dose was given at ≥15 months (23).

Data analysis.

Data were summarized using Microsoft Excel and analyses were performed using Stata Version 10.0 (Statacorp) to summarize case characteristics, clinical management, complications, and outcomes.

Human subjects protection.

The study protocol was approved by the Institutional Review Boards for the Alaska Area of the Indian Health Service and the Centers for Disease Control and Prevention. Approval was also obtained from the Yukon Kuskokwim Health Corporation, the Alaska Native Tribal Health Consortium, and the Southcentral Foundation.

Results

Identification of invasive Hia infections

Of 89 children under 10 years with invasive *Haemophilus influenzae* infections first identified from January 2002 to July 2014, 36 (40%) were identified with invasive Hia disease, giving an overall estimated annual incidence of 2.7 cases of invasive Hia infection per 100,000 children aged under 10 years of age in Alaska. Hia was detected in blood in 29 children, including in blood and CSF in 11 children, and in blood and joint aspirate in 2 children (Table 2). In 7 children without Hia detected in blood, Hia was detected in CSF in 2 children, from joint or soft tissue abscesses in 3 children, from pleural fluid in 1 child, and from lung tissue autopsy in 1 child. Overall, 32 children had Hia isolated by bacterial culture, with all isolates susceptible to ampicillin and ceftriaxone. In 4 other children Hia was detected by PCR—from blood, CSF, pleural fluid, or soft tissue abscess.

Background case characteristics

Of the 36 children with invasive Hia infections, 32 children (89%) were less than 18 months of age, including 27 infants (75%), and all children were more than 3 months of age. All children except two (94%) were of Alaska Native race (Table 2), including 33 children under 5 years of age, giving an annual incidence rate in Alaska Native children aged under 5 years of 17.5 per 100,000. All except two children (94%) were resident in an Alaskan village, mostly in the Yukon-Kuskokwim Delta area of southwest Alaska (Table 2). Underlying medical conditions reported in 11 (31%) children included: chronic lung disease (7 children); documented immune dysfunction or conditions associated with immune suppression (4 children); developmental neurological disease (3 children); and possible

underlying cardiovascular disease (3 children)—a reported mild systolic murmur or pulmonary stenosis. Age appropriate vaccination against Hib was documented in 32 children (89%).

Clinical diagnosis

Overall, 27 children (75%) presented to a health facility within 2 days of symptom onset; later presentation reflected a biphasic illness—an initial relatively mild illness followed by clinical deterioration with more focal symptoms and signs. There were three principal clinical syndromes: meningitis (15 children); pneumonia (10 children); and bone, joint, or soft tissue infections (10 children). One child was diagnosed with pneumonia and meningitis, one with osteomyelitis and meningitis; and one with pneumonia and septic arthritis (Table 2). In 4 remaining children no focus of infection was found to account for invasive infection.

Of 15 children diagnosed with Hia meningitis, 2 initially presented with a stiff neck, bulging fontanelle, or drowsiness. Hia meningitis was confirmed in 13 children by Hia isolated from CSF (12 children) or detected by PCR (1 child); two other children diagnosed with Hia meningitis had Hia bacteremia with clinical meningitis and either diffuse leptomeningeal enhancement on MRI, or consistent CSF abnormalities. For 13 CSF specimens tested, CSF leucocyte count was >100 cells/μL, protein was >50mg/d, and 11 samples appeared turbid; information on CSF glucose was incomplete. Of 10 children diagnosed with pneumonia, 9 had radiologic evidence.

Of 10 children with bone, joint and soft tissue infections, 3 were diagnosed with septic arthritis and bacteremia, 2 with septic arthritis alone, 1 with bacteremia and osteomyelitis on MRI, 3 with soft tissue abscesses (2 also with bacteremia), and 1 other child with cellulitis and bacteremia.

Initial outcomes

Of the 36 children identified with invasive Hia infections, 3 children were considered to have mild illness and were monitored at a local health clinic, and 31 children were admitted to hospital, including 11(35%) admitted to intensive care (Table 3). Two children died from Hia infection before hospital admission. A health aide found a six-month-old boy in cardiopulmonary arrest on arrival at the child's home, and after unsuccessful resuscitation efforts, Hia was detected at autopsy from lung tissue. A four-month-old girl developed a tonic-clonic seizure one day after a fever, and was medically evacuated from her village within several hours, but died during the flight despite resuscitation efforts; Hia was later isolated from CSF (Table 4).

Two other children died from Hia after admission to intensive care (Table 4). An eight-month-old boy presented with fever and a seizure 5 days after developing a mild illness with otitis media, but died a few hours after admission to intensive care, and Hia was isolated on blood culture. The other child was a five-month-old boy with confirmed Hia meningitis, who developed fever, irritability and nausea and presented on the same day. After a complicated hospital course including 17 days in intensive care with pneumonia and repeated seizures, he

died 4 days after discharge; a medical examiner report concluded that Hia infection was the cause of death.

Clinical management

For 33 children who did not present in cardiopulmonary arrest, appropriate antimicrobial agents were administered a median of 1 day after presentation to a local health facility. A treatment delay beyond 2 days in 9 children reflected initial presentation with a milder illness before onset of cough or cellulitis. Six children were switched early from intravenous to oral medication following clinical improvement. None of the children who received less than the recommended duration of antimicrobials died or were reported to have sequelae during follow up.

Hydrocephalus or a subdural collection was reported in 5 of 15 children with meningitis, and three of these children had neurosurgical procedures—a Burr hole, ventricular shunt, or craniectomy as part of the management of mastoiditis and cerebral empyema. Eight other children received surgical drainage of joint or soft tissue abscesses. Four children had strokes, 3 in the middle cerebral artery distribution and 1 in the frontoparietal distribution. At hospital discharge, 8 other children had complications: 6 children with motor deficits or hearing loss, and 2 children with limited movement following septic arthritis. Medical evacuation flights were required to access definitive clinical management for 25 children, and 11 additional flights were needed for hospital transfers. On average, each child required a medical transfer flight from a village or hub hospital, hospital admission for a median of 11 days, and 1 in 3 children required surgical procedures.

Late sequelae

In addition to the 4 children who died from Hia infection, another child died of an unrelated illness six months after the episode of Hia, and 26 of the remaining 31 children had documented clinical evaluations at least 1 year after the initial episode. At one year, 4 children had ongoing motor or speech deficits after stroke; another child had developmental delay affecting speech after hydrocephalus requiring a ventriculoperitoneal shunt (Table 4). Three children developed recurrent invasive Hia infection after the initial episode: a 6-month-old girl diagnosed with chronic lung disease who developed Hia meningitis 4 months after completing therapy for Hia pneumonia; a 7-month-old boy who was previously well developed a recurrence of septic arthritis 4 months after receiving drainage and 20 days' antimicrobial therapy for Hia infection in the same joint; and a 10-month-old girl with a mild pulmonary valve murmur who developed Hia meningitis 4 months after Hia septic arthritis. Local physicians had prescribed chemoprophylaxis to close contacts of this child after the first episode, and after the recurrent episodes for the other children.

Discussion

We identified 36 children under 10 years of age with a first episode of invasive Hia infection between 2002 and 2014, in 75% of cases between the ages of 3 months and 1 year. These children were almost entirely from Alaska Native populations living in remote villages, predominantly in the Yukon Kuskokwim Delta region of southwest Alaska. Consistent with

a previous study of the emergence of Hia in Alaska(9), Alaska Native children under 5 years experienced rates of invasive Hia infections higher than rates of invasive Hib disease after Hib vaccine(6), and nearly one third of the rate of invasive pneumococcal disease after the introduction of pneumococcal conjugate vaccine(24).

For children with invasive Hia infections, the overall outcomes were poor. By a year after the initial episode, 9 children (25%) had either died or suffered ongoing complications as a result. Whereas children with pneumonia or bone, joint or soft tissue infections tended to make a full recovery, all except one child with long-term sequelae were diagnosed with Hia meningitis or bacteremia. Of the 18 children diagnosed with meningitis or bacteremia, over 40% died or developed neurological sequelae from stroke or other complications of meningitis, such as hydrocephalus and empyema.

Our study was strengthened by using a population based surveillance system to identify cases, and by detailed review of medical charts that included details of background illness, clinical management, and late sequelae. We found that invasive infections could not be attributed to underlying illness in 75% of children, and the majority of children with severe outcomes did not have documented underlying conditions. Neither could severe outcomes be explained by a delay in accessing local healthcare or in initiating appropriate antimicrobial therapy. After clinical deterioration, children were rapidly transferred to hospitals from village health facilities. This required substantial resources, including medical evacuation flights for most children, and hospitalization for an average of more than 10 days.

We found that over 40% of children with invasive Hia infection presented with meningitis, sometimes resulting in severe neurologic sequelae. Although our descriptions of invasive Hia infections (Table 1) are consistent with others (2, 15, 16, 18, 19, 25, 26), our case-fatality rate of 11% is higher than the 0 to 6% reported in other population-based studies (16, 18, 19), with the exception of a study reviewing cases managed by tertiary pediatric centers in which 4 of 25 children (16%) died (15). All 9 children with severe outcomes in our study were infants, mostly aged 6 months or younger, and one possible explanation for the higher case-fatality rate in Alaska is the younger median age of 7 months compared with these studies (16, 18, 19).

Another potential explanation is that Hia strains in Alaska were more virulent, but previous analyses suggest similarity with strains in Canada (2, 4), and the bexA deletion, which has been associated with increased virulence, was not found in Alaskan isolates (9). Mortality rates for meningitis, bacterial sepsis and pneumonia are high in Alaska Native populations compared with other populations in the United States(27). It is not known whether other risk factors for respiratory infections in indigenous populations (28) such as poor indoor air quality and household crowding could also lead to increased Hia severity through a larger mean inoculum or diminished host defenses. Although Alaska Native populations have local access to an extensive tribal healthcare system, it is also possible that the remoteness of the populations increased the time until intensive care admission for some children who presented in a critical condition.

Overall, we found the demographics, clinical characteristics and case severity of invasive Hia infections to be very similar to historic data describing invasive Hib infections in Alaska during the 1980s. Hib cases at that time were similar to these Hia cases with a median age of 8 months, two thirds of cases male, 47% with meningitis, and a case-fatality rate of 6.3% (5). Another study also noted the similarity between clinical disease caused by Hia and Hib (2). In the present study, all 9 children who died or experienced sequelae were between 3 and 9 months of age at presentation, and, of the 4 oldest children over 18 months, 3 had underlying illness. The higher proportion of invasive Hia and increased complications in infants is similar to Hib (1) and may also be caused by age-dependent limitations in T cell responses, which an Hia conjugate vaccine could address.

We found that children with invasive Hia infections presented with a mild and non-specific illness which sometimes progressed rapidly. Providers serving remote and vulnerable populations should therefore be aware of Hia, to ensure accurate diagnosis and appropriate clinical management. However, we found that severe outcomes occurred even with timely investigation, antimicrobial therapy, surgery, and supportive care. In addition, three children developed recurrent invasive Hia infections, for one child after antimicrobial chemoprophylaxis was prescribed to close contacts. Although some providers working in highly affected populations offer chemoprophylaxis to case contacts (29), this is not included in current recommendations (8) since, in contrast to Hib, direct transmission between cases of invasive Hia infections has not been reported (8). For children presenting with invasive Hia disease, further studies would help determine best practice for clinical management and the potential role of chemoprophylaxis.

A vaccine of similar efficacy to the Hib vaccine could prevent future cases of invasive Hia infections. Studies are underway in Canada to develop candidate vaccines (30–32). One limitation to developing a vaccine against Hia is likely to be the limited population affected by this disease and subsequent problems attracting a commercial manufacturer. Therefore, vaccine development efforts could be supported by a better understanding of the overall Hia disease burden worldwide. Improved epidemiologic surveillance is needed to improve understanding of global distribution and to identify populations in which Hia may be emerging (19). Surveillance systems with capacity to monitor *S. pneumoniae* or Hib could also identify other serotypes of *H. influenzae* and genomic surveillance could help identify strains with increased incidence or responsible for poor outcomes. Further population-based studies are needed to describe case-severity in different settings, to characterize risk factors for severe disease. This study indicates that, to prevent morbidity and mortality from Hia in affected populations, a vaccine would need to protect 3 to 9 month year old infants in affected populations from invasive Hia disease.

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Table 1:

Population Studies of the Severity of Invasive *Haemophilus influenzae* type a (Hia) Disease in Children

Study Author (Year)	**Bender (2010)**	**McConnell (2007)**	**Millar (2005)**	**Rotondo (2013)**
Study location (years)	Utah (1998–2008)	Canada(1996–2001)	Navajo, White Mountain Apache (1988–2003)	Canada (2000–2010)
Case ascertainment	Microbiology and hospital reports	Pediatric tertiary care centers	Active surveillance system	Public health laboratory passive surveillance
No. Isolates Hia / Serotyped *Haemophilus* isolates (%)	23/68 (34%)	25/147 (17%)	76/222 (34%)	72/128 (56%)
Estimated incidence per 100,000 children	0.8–2.6 (under 5 years)	2.3–418 (under 5 years)	20.2 (under 5 years)	4.6 (all ages)
Median age	11 months	8.5 months	12 months	-
Hia meningitis	13 (57%)	13 (52%)	38 (50%)	27 (37%)
Hospital admission	22 (96%)	25 (100%)	60 (79%)	62 (90%)
Intensive care admission	-	10 (40%)	-	-
Sequelae at discharge	-	6 (24%)	5 (7%)	-
Died	0 (0%)	4 (16%)	2 (3%)	4 (6%)

Table 2:

Characteristics of 36 Children with Invasive *Haemophilus influenzae* type a (Hia) Disease in Alaska, 2002–2014

Characteristic	Value* (n=36)
Age, median months (range)	7 (3–98)
Male sex	24 (67%)
American Indian / Alaska Native	34 (94%)
Resident in remote village	34 (94%)
Medical history	
Underlying illness†	11 (31%)
Preterm birth (<37 weeks)	3‡ (8%)
Onset to presentation, median days (range)	1 (0–10)
Specimen Source	
Blood only	16 (44%)
lood and CSF	11 (30%)
lood and joint	2 (6%)
CSF only	2 (6%)
Joint only	2 (6%)
Other source§	3 (8%)
Diagnosis¶	
Meningitis	15 (42%)
Pneumonia	10 (28%)
Bone or joint infection	6 (17%)
Soft tissue collection	4 (11%)
Unknown source of infection	4 (11%)

*Data are no. (%) of children, unless otherwise indicated.

†Defined as any chronic illness listed at the time of clinical presentation

‡Born ≥35 weeks gestation

§Aspiration from soft tissue collection (n=1), pleural fluid (n=1), lung tissue at autopsy (n=1)

¶Some cases had overlapping diagnoses of meningitis with pneumonia (n=1), meningitis with bone or joint infection (n=1), or pneumonia with bone or joint infection (n=1)

Table 3:

Management and Outcome of 36 Children with Invasive *Haemophilus influenzae* type a (Hia) Disease in Alaska, 2002–2014

Site of Infection	Meningitis* (n=15)†	Pneumonia* (n=10)†	Bone, Joint, or Soft Tissue* (n=10)†	Any Site* (n=36)
Level of care				
Died before or during presentation to care	1 (7%)	0 (0%)	0 (0%)	2 (6%)
Local clinic only	0 (0%)	2 (20%)	0 (0%)	3 (8%)
Hospital, non-ICU	5 (33%)	6 (60%)	10 (100%)	20 (56%)
ICU, not ventilated	5 (33%)	0 (0%)	0 (0%)	5 (14%)
ICU, ventilated	4 (27%)	2 (20%)	0 (0%)	6 (17%)
Transfer to tertiary hospital	6 (40%)	1 (10%)	6 (60%)	12 (33%)
Length of stay, median days (range)‡	12.5 (3–48)	8.5 (3–48)	11.5 (4–18)	11 (1–48)
Time to antibiotics, median days (range)‡	1 (0, 7)	1 (0, 7)	1 (0, 9)	1 (0, 9)
Completed recommended duration and route of therapy‡	13 (100%)	6 (60%)	8 (80%)	26 (79%)
Surgery to treat Hia infection	3 (20%)	1 (10%)	8 (80%)	11 (31%)
Died from Hia infection	2 (13%)	0 (0%)	0 (0%)	4 (11%)
Complications at discharge	9 (60%)	3 (30%)	2 (20%)	12 (33%)
Complications 1 year after Hia infection	4 (27%)	2 (20%)	0 (0%)	5 (14%)
Recurrent episode of Hia	0 (0%)	1 (10%)	2 (10%)	3 (8%)

*Value represents number of children (% total) unless otherwise stated.

†Diagnosis categories not mutually exclusive.

‡Excludes children who died before or during presentation to care.

Table 4:

Background, Presentation, Management and Complications of 9 Children with Invasive *Haemophilus influenzae* type a (Hia) Disease in Alaska who Died or Had Ongoing Complications after 1 Year, 2002–2014

Case	Age in months, sex	Underlying condition	Presentation (duration)	Site	Complications, Other Management	Sequelae by 1 year
1	6, male	Hypohydratic ectodermal dysplasia	Unknown	Not localized (Hia from lung tissue on autopsy *)	Cardiac arrest in community (witnessed by village health aide)	Died
2	4, female	No	Fever and seizure (1 day)	Meningitis (Hia in CSF on autopsy)	Cardiac arrest in flight (managed by evacuation team)	Died
3	8, male	No	Fever and seizure (5 days)	Not localized (Hia on blood culture)	Intensive care, ventilated	Died (cardiac arrest in intensive care)
4	5, male	No	Fever, nausea, irritability (1 day)	Meningitis (Hia in CSF)	Intensive care, ventilated	Died (died 4 days after discharge) †
5	5, male	Born at 36 weeks	Cough, fever (1 week)	Meningitis (Hia in blood, CSF)	Transfer to specialist center, Burr hole for frontoparietal empyema	Speech delay
6	9, male	No	Seizure after prodrome (5 days)	Meningitis (Hia in blood, CSF)	Communicating hydrocephalus, ventriculo-peritoneal shunt	Hearing loss, possible ongoing developmental delay
7	8, male	Recurrent pneumonia	Cough, fever (1 day)	Pneumonia (Hia in pleural fluid *)	Middle cerebral artery stroke	Hemiparesis
8	6, male	No	Lethargy, bulging fontanelle after prodrome (3 days)	Meningitis (Hia in blood, CSF)	Middle cerebral artery stroke	Hemiparesis, hearing loss
9	6, male	Born at 35 weeks	Lethargic following prodrome	Meningitis ‡ (Hia in blood)	Middle cerebral artery stroke	Hemiparesis, hearing loss, speech delay

* PCR positive only

† Chief Medical Examiner attributed this death to Hia

‡ Radiological evidence of meningitis

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