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# Brain Abscess and Stroke in Children and Adults With Hereditary Hemorrhagic Telangiectasia

## Analysis of a Large National Claims Database


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## Abstract

### Background and Objectives

Hereditary hemorrhagic telangiectasia (HHT) is an inherited disease associated with pathogenic variants in transforming growth factor- $\beta$  signaling pathway–related genes, resulting in abnormal vascular development in various organs. Brain arteriovenous malformations (AVMs) may lead to intracranial hemorrhage, and brain abscess or ischemic stroke may result from right to left shunting via pulmonary AVMs. We aimed to investigate the risk for these severe complications in both adults and children with HHT.

### Methods

We conducted a case-control study among participants aged 1–64 years in the MarketScan Commercial (2006–2019) and Multistate Medicaid Databases (2011–2019). We identified cases with HHT using *International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification (ICD-9/10)* diagnosis codes (ICD-9-CM 448.0, ICD-10-CM I78.0). Control patients without HHT coding were frequency matched 10:1 to patients with HHT by age, duration of insurance enrollment, sex, and Medicaid status. Outcomes of interest (brain abscess, stroke, and intracranial/subarachnoid hemorrhage) were identified using the appropriate ICD-9/10 diagnosis codes. We calculated incidence and standardized rates of the various outcomes and compared rate ratios (RRs) between HHT cases and controls.

### Results

A total of 5,796 patients with HHT, of whom 588 were children (age younger than 16 years), were matched with 57,960 controls. There was an increased incidence of brain abscesses in HHT cases compared with controls, with an RR of 35.6 (95% CI 15.4–82.5). No brain abscesses were recorded in children aged 15 years or younger. Hemorrhagic strokes/subarachnoid hemorrhages were more common in HHT cases, with an RR of 4.01 (95% CI 2.8–5.7) in adults and 60.2 (95% CI 7.2–500.4) in children. Ischemic strokes were also more common in cases, with an RR of 3.7 (95% CI, 3.0–4.5) in adults and 70.4 (95% CI 8.7–572.3) in children.

### Discussion

We observed a much higher incidence of severe CNS vascular complications in patients with HHT, particularly in children. Although a higher incidence of brain abscesses was noted in adult patients with HHT, no brain abscesses were recorded in children, a result that may be considered when surveillance recommendations for this population are revisited.

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## Glossary

**AVM** = arteriovenous malformation; **HHT** = hereditary hemorrhagic telangiectasia; **RR** = rate ratio; **ICD-9/10-CM** = *International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification*; **PYO** = person years of observation; **RR** = rate ratio.

Hereditary hemorrhagic telangiectasia (HHT) is an under-recognized genetic disorder of vasculature that is caused by pathogenic sequence variations in the transforming growth factor- $\beta$  signaling pathway.<sup>1-3</sup> These alterations occur in *endoglin*, *activin A receptor-like kinase*, *SMAD4*, and others, which are transmitted in an autosomal dominant fashion with variable penetrance. Variations lead to a disruption in the balance between proangiogenic and antiangiogenic signals that are necessary for normal vascular development.

The diagnostic criteria reflect the common clinical symptoms, which include recurrent spontaneous epistaxis, mucocutaneous telangiectasia, solid organ arteriovenous malformations (AVMs) typically in the lung,<sup>4</sup> brain,<sup>5</sup> spinal cord, or liver, and a first-degree relative with HHT.<sup>6</sup> Epistaxis may occur daily and can lead to anemia and chronic blood transfusion dependence. Mucocutaneous telangiectasia is generally only of cosmetic concern, although telangiectasias throughout the GI tract may also contribute to iron deficiency anemia and transfusion dependence. AVMs may result in intracranial hemorrhage when present in the brain, pulmonary hemorrhage when present in the lung, and high output heart failure when present in the liver. Brain abscess or ischemic stroke may also occur because of right to left shunting through pulmonary AVMs.<sup>7</sup>

Although the overall prevalence of HHT is estimated to be between 1:5,000 and 1:8,000 in various populations,<sup>8</sup> precise estimates of the risk of complications from HHT have been difficult to ascertain because of both the rarity of HHT and the observation that most people with HHT have not yet been diagnosed. This has been particularly true for children with HHT.

Claims databases have been used to describe the epidemiology of less common diseases. One such study<sup>9</sup> of HHT included the population of Alberta, Canada, with approximately 4 million people, in which the incidence of stroke in patients with HHT was examined. These authors found a significantly higher incidence rate of stroke in patients with HHT but did not assess the occurrence of brain abscess and did not specifically assess the risk in children.

Using administrative claims data, we compared the risk of stroke and brain abscess in both adult and pediatric patients with HHT with control populations in the databases.

## Methods

### Identification of the HHT and Control Populations

We identified persons aged 1–64 years in the IBM MarketScan Commercial Database from January 1, 2006, to

December 31, 2019, and from January 1, 2011, to December 31, 2019, in the MarketScan Medicaid Database with an HHT diagnosis using *International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification* (ICD-9/10-CM) diagnosis codes (ICD-9-CM 448.0, ICD-10-CM I78.0). To establish the diagnosis of HHT, coding was required on at least 1 inpatient facility claim and/or 2 or more outpatient/provider claims spaced at least 30 days apart. Diagnostic claims (e.g., laboratory, diagnostic radiology) were not used to identify HHT to avoid identification of rule-out conditions.<sup>10</sup>

Control persons aged 1–64 years without HHT were identified based on no coding for HHT during the period of health insurance enrollment. For the purpose of comparison with the HHT population, controls were frequency matched 10:1 to individuals with HHT by age (in 5-year categories), duration of health insurance enrollment (per completed year), insurance enrollment start year, sex, and Medicaid status.

### Identification of Underlying Conditions

Comorbidities were defined using the classification of Elixhauser et al.<sup>11</sup> and the pediatric chronic conditions classification of Feudtner et al.,<sup>12</sup> including conditions coded at any time during the medical insurance enrollment dates. Comorbidities, which included various malignancies and anemia, were defined as above for HHT, requiring coding on at least 1 inpatient facility claim and/or 2 or more outpatient/provider non-diagnostic claims spaced at least 30 days apart. In addition, the mean number of clinic visits per year was determined per person using Current Procedural Terminology, Fourth Edition codes 99201–99215, 99241–99245, 99381–99386, and 99391–99396 as a measure of overall health care utilization.

### Identification of Outcomes

Outcomes were identified at any time during health care enrollment using 1 or more diagnosis codes on nondiagnostic claims, including brain or CNS abscess, hemorrhagic stroke, ischemic stroke (includes embolic/thromboembolic stroke), and subarachnoid hemorrhage. The specific diagnostic codes for these outcomes are listed in Table 1.

For acute ischemic and hemorrhagic stroke, brain/CNS abscess, and subarachnoid hemorrhage, coding was required during an inpatient admission of at least 2 days or in an inpatient admission with shorter length of stay with a discharge status of died. Hemorrhagic stroke data included cases in which there was either a hemorrhagic or a subarachnoid stroke, or both in the same patient, as some cases were entered as having both a subarachnoid and hemorrhagic stroke. To avoid double counting any single patient, hemorrhagic stroke

**Table 1** ICD-9-CM and ICD-10-CM Codes Used for Outcome Variables

Condition	ICD-9-CM	ICD-10-CM
Brain/CNS abscess	324.0, 324.9	G06.0, G06.2
Hemorrhagic stroke	431, 432	I61, I62.00, I62.01 I62.1 I62.9
Ischemic stroke	433, 434	I63
Subarachnoid hemorrhage	430	I60

and subarachnoid hemorrhage were combined into one outcome variable for analysis.

### Statistical Analyses

Descriptive statistics were performed for the HHT case and control populations for underlying comorbidities and the number of office visits per year. The prevalence rate of HHT was calculated based on the person time of observation (per 100,000 person years of observation [PYO]), using the medical insurance enrollment start and end dates for the entire population of persons aged 1–64 years in the MarketScan Commercial and Medicaid databases.

Incidence and prevalence rates per 100,000 PYO were calculated overall and for subgroups of children, defined as age 1–15 years and adults 16–64 years, for the individual outcomes of interest in the HHT case and control populations, respectively. The age of 16 years was used to define adulthood for consistency with other HHT studies.<sup>13–15</sup> In addition, rates were calculated for various age subgroups. Comparisons of the standardized rates per 100,000 PYO between the HHT and frequency-matched control groups were performed using PROC STD RATE, with calculation of rate ratios (RRs). *p* value <0.05 was considered statistically significant in comparison of incidence and prevalence ratios. All statistical analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC). Data acquisition and analysis was carried out through the Center for Administrative Data Research, which is supported in part by the Washington University Institute of Clinical and Translation Sciences from the National Center for Advancing Translation Science of the NIH.

### Standard Protocol Approvals, Registrations, and Patient Consents

This study was declared a nonhuman study by the WU Human Research Protection Office because of the use of a limited data set with no identifiable information.

### Data Availability

The data underlying this article were provided by IBM MarketScan Commercial Database under license. Data will be shared on reasonable request to the corresponding author with permission from IBM MarketScan Commercial Database.

## Results

A total of 5,796 patients with HHT were identified from the MarketScan Commercial and Multistate Medicaid Databases, which included 588 children younger than 16 years.

The control group of frequency-matched patients who were not coded for HHT during their insurance enrollment observation time included a total of 57,960 patients, of whom 5,880 were children younger than 16 years. Approximately 9% of the HHT and the control patients were on Medicaid, and 91% were not enrolled in Medicaid. Sixty-four percent of patients were female and 36% were male in both the case and in the control groups.

### Comorbidities and Medical Office Visits

HHT cases had increased risk for various types of malignancies and chronic anemias (eTable 1, [links.lww.com/WNL/C763](https://links.lww.com/WNL/C763)) compared with matched controls—a matter worthy of a discussion which extends beyond the scope of this paper. In addition, patients with HHT were much more likely to be seen 21 or more times a year, compared with controls (eTable 2, [links.lww.com/WNL/C764](https://links.lww.com/WNL/C764)).

### Brain Abscess

A significantly higher incidence of brain abscess was found in patients with HHT compared with the control patients (Table 2). Brain abscess was identified in 25 adult patients with HHT, a rate of 94.6 cases per 100,000 PYO, compared with 7 cases of brain abscess in the control group (2.4 cases per 100,000 PYO), resulting in an RR of 35.6 (95% CI 15.4–82.5). In children aged 15 years and younger, there were no cases of brain or CNS abscess recorded in the control group nor were there any cases in those with HHT.

Grouped by decade, an examination of the data by age at onset of brain abscess was performed. No clear peak age at onset of brain abscess was apparent, and the risk ratios were significantly elevated in each age bracket (Table 3).

### Stroke

Stroke was found more commonly in adult patients with HHT compared with the control population (Table 2). Hemorrhagic stroke or subarachnoid hemorrhage occurred in 43 adults with HHT (162.9 cases per 100,000 PYO), compared with controls (40.6 cases per 100,000 PYO) in which there were a total of 107 cases. The calculated incidence RR of hemorrhagic stroke in HHT cases was 4.01 (95% CI 2.8–5.7).

The RR for ischemic stroke in adults with HHT compared with control cases was 3.7 (95% CI 3.0–4.5) occurring in 120 adult patients with HHT compared with 329 control patients (458.1 vs 125.3 cases per 100,000 PYO).

In comparing children with HHT with frequency-matched controls, both hemorrhagic and ischemic strokes were more common. The RR for hemorrhagic stroke/subarachnoid

**Table 2** Outcomes in HHT Cases vs Controls

	Cases		Controls		Rate ratio (95% CI)	p Value
	Frequency (%) <sup>a</sup>	Rate <sup>b</sup>	Frequency (%) <sup>a</sup>	Rate <sup>b</sup>		
<b>All patients (5,796 cases, 57,960 controls)</b>						
Brain/CNS abscess	25 (0.43)	84.4	7 (0.01)	2.4	35.6 (15.4–82.3)	<0.0001
Hemorrhagic stroke or subarachnoid hemorrhage	49 (0.85)	165.8	108 (0.19)	36.6	4.5 (3.2–6.4)	<0.0001
Ischemic stroke	127 (2.19)	432.6	330 (0.57)	112.1	3.9 (3.01–4.7)	<0.0001
<b>Age &lt;15 y (588 cases, 5,880 controls)</b>						
Brain/CNS abscess	0 (0.00)	0.0	0 (0.00)	0.0	n/a	
Hemorrhagic stroke or subarachnoid hemorrhage	6 (1.02)	189.7	1 (0.02)	3.2	60.2 (7.2–500.4)	<0.0001
Ischemic stroke	7 (1.19)	221.7	1 (0.02)	3.2	70.4 (8.7–572.3)	<0.0001
<b>Age &gt;15 y (5,208 cases, 52,080 controls)</b>						
Brain/CNS abscess	25 (0.48)	94.6	7 (0.01)	2.7	35.6 (15.4–82.5)	<0.0001
Hemorrhagic stroke or subarachnoid hemorrhage	43 (0.83)	162.9	107 (0.21)	40.6	4.0 (2.8–5.7)	<0.0001
Ischemic stroke	120 (2.30)	458.1	329 (0.63)	125.3	3.7 (3.0–4.5)	<0.0001

Abbreviation: HHT = hereditary hemorrhagic telangiectasia.

<sup>a</sup> Frequency is presented as number of persons with an observed event.

<sup>b</sup> Rates are presented as number of events per 100,000-person years of observation.

hemorrhage in children was 60.2 (95% CI 7.2–500.4). There were 6 cases of hemorrhagic stroke/subarachnoid hemorrhage (189.7 cases per 100,000 PYO) in children with HHT vs 1 case in matched control patients (3.2 cases per 100,000 PYO).

The RR for ischemic stroke in children with HHT was 70.4 (95% CI 8.7–572.3). There were 7 cases of ischemic stroke in children with HHT (221.7 cases per 100,000 PYO) vs 1 case in controls (3.2 cases per 100,000 PYO).

When broken down into 10-year interval age groups (Tables 4 and 5), incidence rates for both hemorrhagic and ischemic (embolic/thromboembolic) stroke demonstrate increases with age in frequency-matched controls. This increase, however, was

not witnessed as clearly in stroke rates among HHT cases, particularly involving hemorrhagic stroke rates, which seemed to be non-age-related in this population. The RRs for both types of strokes, however, were consistently higher in HHT cases compared with controls, across all age groups. The highest RR for hemorrhagic strokes was 89.6 (95% CI, 11.3–707.5) and was seen in the 16–25 years age group, and the highest RR for ischemic stroke was 69.8 (8.6–567.7) in the 1–15 years age group.

## Discussion

Complications from HHT such as stroke and brain abscess, although rare, are potentially serious and may be life-threatening. Estimates of the risk of these complications have been difficult to quantify because of the relative rarity of HHT and its diagnostic

**Table 3** Brain/CNS Abscess in Adult HHT Cases vs Controls by Age

Age group (y)	Cases				Controls				Rate ratio (95% CI)	p Value
	N	PYO	Frequency (%) <sup>a</sup>	Rate <sup>b</sup>	N	PYO	Frequency (%) <sup>a</sup>	Rate <sup>b</sup>		
16–25	457	2,214	2 (0.51)	90.3	4,570	22,051	0 (0)	0.0		
26–35	607	2,639	2 (0.33)	75.8	6,070	26,138	1 (0.02)	3.8	19.8 (1.8–218.5)	0.015
36–45	981	5,077	2 (0.2)	39.4	9,810	50,456	0 (0)	0.0		
46–55	1,625	9,172	10 (0.62)	109.0	16,250	91,350	2 (0.01)	2.2	49.8 (10.9–227.3)	<0.0001
56–64	1,538	7,394	9 (0.59)	121.7	15,380	73,504	4 (0.03)	5.4	22.4 (6.9–72.6)	<0.0001

Abbreviations: HHT = hereditary hemorrhagic telangiectasia; PYO = person years of observation.

<sup>a</sup> Frequency is presented as number of persons with an observed event.

<sup>b</sup> Rates are presented as number of events per 100,000 PYO.

**Table 4** Hemorrhagic Strokes in Adult HHT Cases vs Controls by Age

Age group (y)	Cases				Controls				Rate ratio (95% CI)	p Value
	N	PYO	Frequency (%) <sup>a</sup>	Rate <sup>b</sup>	N	PYO	Frequency (%) <sup>a</sup>	Rate <sup>b</sup>		
16–25	457	2,214	9 (1.97)	406.5	4,570	22,051	1 (0.02)	4.5	89.6 (11.3–707.5)	<0.0001
26–35	607	2,639	6 (0.99)	227.4	6,070	26,138	3 (0.05)	11.5	19.8 (4.9–79.2)	<0.0001
36–45	981	5,077	3 (0.3)	59.1	9,810	50,456	12 (0.12)	23.8	2.5 (0.7–8.8)	0.159
46–55	1,625	9,172	12 (0.74)	130.8	16,250	91,350	43 (0.26)	47.1	2.8 (1.5–5.3)	0.0017
56–64	1,538	7,394	13 (0.8)	175.8	15,380	73,504	48 (0.31)	65.3	2.7 (1.5–5.0)	0.0015

Abbreviations: HHT = hereditary hemorrhagic telangiectasia; PYO = person years of observation.

<sup>a</sup> Frequency is presented as number of persons with an observed event.

<sup>b</sup> Rates are presented as number of events per 100,000 PYO.

underrecognition and underrepresentation in some databases.<sup>13</sup> In addition, the low frequency of events such as stroke and abscess necessitate examination of large data sets. The data included in the MarketScan database allow for capture of these occurrences and allow for the calculation of such risks.

Brain abscess was found to be more common in patients with HHT compared with controls. The RR of 35.6 confirms the clinical experience of many physicians<sup>16–19</sup> caring for these patients, as well as the community of those with HHT and their families.<sup>20</sup> This rate is similar to the adjusted odds ratio reported by Donaldson et al.<sup>21</sup> of 30 in their analysis of 675 patients with HHT from an UK primary care database of 3.5 million individuals.

Interestingly, no cases of brain abscess were present in children with HHT nor in the controls. Scattered case reports of brain abscess in HHT do exist in the literature, but are rare in children. Roberts et al.<sup>22</sup> reported a single case of a 3-year-old male and Press and Ramsey<sup>23</sup> reported an 11-year-old child, in a cohort of 31 cases, of whom 30 were adults. In addition to the presence of a pulmonary AVMs, some of the risk factors for developing abscesses in patients with HHT include dental infections<sup>24</sup> (both treated and untreated) and hypoxemia, both of which may be less common in children and which,

therefore, may contribute to the lower rates. These data suggest that recommendations for the prevention of brain abscess, which include both the treatment of pulmonary AVMs and use of antibiotic prophylaxis for invasive dental procedures, for example, remain important in adult patients with HHT but may not be as necessary in children. More data are needed before recommendations can be made with confidence.

The relative proportion of stroke type (ischemic vs hemorrhagic) was roughly 1:1 in children, whereas there were approximately 3 times as many ischemic (versus hemorrhagic) strokes in adults in both the control group and those with HHT.

The RR for hemorrhagic stroke/subarachnoid hemorrhage was 60.2 and for ischemic (embolic/thromboembolic) stroke was 70.4, both indicating an increased risk for children with HHT compared with the frequency-matched controls. It is known that adults with HHT are at risk for stroke, but this dramatic increase in the incidence risk rates for children demonstrated here is not as well recognized. One possible reason for the lower RRs in adult patients may be the observation that adults, with or without HHT, suffer from strokes that are unrelated to HHT at much higher rates than

**Table 5** Ischemic Strokes in Adult HHT Cases vs Controls by Age

Age group (y)	Cases				Controls				Rate ratio (95% CI)	p Value
	N	PYO	Frequency (%) <sup>a</sup>	Rate <sup>b</sup>	N	PYO	Frequency (%) <sup>a</sup>	Rate <sup>b</sup>		
16–25	457	2,214	5 (1.1)	225.8	4,570	22,051	1 (0.02)	4.5	49.8 (5.8–426.2)	0.0004
26–35	607	2,639	4 (0.66)	151.6	6,070	26,138	7 (0.12)	26.8	5.6 (1.7–19.3)	0.0057
36–45	981	5,077	14 (1.4)	275.7	9,810	50,456	27 (0.28)	53.5	5.1 (2.7–9.8)	<0.0001
46–55	1,625	9,172	38 (2.3)	414.3	16,250	91,350	117 (0.72)	128.1	3.2 (2.2–4.6)	<0.0001
56–64	1,538	7,394	59 (3.8)	797.9	15,380	73,504	177 (1.15)	240.8	3.3 (2.5–4.4)	<0.0001

Abbreviations: HHT = hereditary hemorrhagic telangiectasia; PYO = person years of observation.

<sup>a</sup> Frequency is presented as number of persons with an observed event.

<sup>b</sup> Rates are presented as number of events per 100,000 PYO.

children. Lehman et al.<sup>14</sup> calculated a pediatric stroke rate of 4.4 per 100,000 children, which is a small fraction compared with the estimated 150 cases per 100,000 of people of all ages with stroke world wide. Indeed, hemorrhagic or ischemic stroke in children are rare in the general population, and patients with HHT are at much higher risk for these severe manifestations with often grim consequences.

Thirteen cases of stroke occurred in children with HHT, but only 2 cases in the controls, although there were 10 times as many patients included in the control group. Further analysis using stratification of adult patients into 10-year interval age groups showed astronomical RR for ischemic and hemorrhagic strokes in young adult patients with HHT, compared with controls. Consequently, when stroke occurs in those younger than 25 years, an evaluation for possible underlying HHT may be considered.

Because patients with HHT with a relatively mild phenotype can remain undiagnosed for years, the high complication rates demonstrated in this study may be somewhat exaggerated because undiagnosed patients without complications were not included in the denominator of our incidence rate calculation. On the other hand, it is possible that some of the controls in this study diagnosed with a CNS complication were in fact patients with undiagnosed HHT, especially in fatal cases which may not undergo a complete evaluation. Larsen et al.<sup>18</sup> showed that 2.5% of patients evaluated for a brain abscess were subsequently diagnosed with HHT, a much higher fraction than the prevalence of HHT in the population (less than 0.02%). The female:male ratio of almost 2:1 in our cohort has been reported by others.<sup>13,25</sup> It has been suggested that women tend to seek medical evaluation more commonly than men and may, therefore, be diagnosed more quickly. The same concept of increased exposure to medical care is also demonstrated in our data showing a higher number of annual medical office visits in patients with HHT compared with controls (eTable 2, [links.lww.com/WNL/C764](https://links.lww.com/WNL/C764)). It is possible that patients with diagnosed HHT have an overall better medical surveillance compared with the general population and that they may also be diagnosed more often with hematologic and oncologic conditions (eTable 1, [links.lww.com/WNL/C763](https://links.lww.com/WNL/C763)), as well as the CNS complications discussed in this study.

The strength of this study is the population-based design allowing examination of a large proportion of the privately insured nonelderly US population. However, there are some potential limitations of this study. First, the inability to link the claims data to direct clinical information precludes the verification of the HHT diagnoses. Second, assignment of specific diagnostic codes is variable in administrative data sets, and therefore, these results likely underestimate the true prevalence of these complications. Finally, these data are limited to privately and Medicaid-insured patients, and the results may not be representative of patients without health insurance coverage.

In summary, the MarketScan database was used to assess complications and associations in patients with HHT. More than 5,000 adults and nearly 600 children were identified with this uncommon disease. RRs for complications were significantly higher for hemorrhagic stroke and ischemic stroke in adults with HHT compared with controls. RRs were also higher in children with HHT for hemorrhagic and ischemic stroke. Brain abscess RRs were significantly higher in adults with HHT compared with controls. However, no cases of brain abscess in children with HHT were present in the database nor in the controls. Taken together, these findings confirm clinical observations that adults with HHT are at higher risk for neurologic complications such as brain abscess, hemorrhage, and stroke. The absence of brain abscesses in children suggests that this complication is rare.

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## Disclosure

The authors report no relevant disclosures. Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures.

## Publication History

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## Appendix Authors

Name	Location	Contribution
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<b>Itay Marmor, MD</b>	Department of Pediatrics, Washington University School of Medicine, St. Louis, MO	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
<b>Kate M. Peacock</b>	Division of Infectious Diseases, Department of Medicine, Washington University School of Medicine, St. Louis, MO	Major role in the acquisition of data; study concept or design; analysis or interpretation of data
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<b>Jessica Zavadil, MD, PhD</b>	Department of Pediatrics, Washington University School of Medicine, St. Louis, MO	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design

Continued



## Appendix (continued)

Name	Location	Contribution
<b>Margaret A. Olsen, PhD, MPH</b>	Division of Infectious Diseases, Department of Medicine, Washington University School of Medicine, St. Louis, MO	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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