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ORIGINAL ARTICLE

Prospective Surveillance of Pediatric Invasive Group A *Streptococcus* Infection

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Background. Invasive group A *Streptococcus* (GAS) disease has an incidence in high-income countries of 3 to 5 per 100 000 per annum and a case-fatality ratio of 10% to 15%. Although these rates are comparable to those of invasive meningococcal disease in Australia before vaccine introduction, invasive GAS disease currently requires reporting in only 2 jurisdictions.

Methods. Data were collected prospectively through active surveillance at the Royal Children's Hospital, Melbourne (October 2014 to September 2016). Isolation of GAS from a sterile site was required for inclusion. Comprehensive demographic and clinical data were collected, and *emm* typing was performed on all isolates. Disease was considered severe if the patient required inotropic support or mechanical ventilation.

Results. We recruited 28 patients. The median age of the patients was 3.5 years (range, 4 days to 11 years). Ten (36%) patients had severe disease. Fifteen (54%) children had presented to a medical practitioner for review in the 48 hours before their eventual admission, including 7 of the 10 patients with severe GAS infection. Complications 6 months after discharge persisted in 21% of the patients. *emm1* was the most common *emm* type (29%).

Conclusion. We found considerable short- and longer-term morbidity associated with pediatric invasive GAS disease in our study. Disease manifestations were frequently severe, and more than one-third of the patients required cardiorespiratory support. More than one-half of the patients attended a medical practitioner for assessment but were discharged in the 48-hour period before admission, which suggests that there might have been a window for earlier diagnosis. Our methodology was easy to implement as a surveillance system.

Keywords. Group A *Streptococcus*; pediatric; sepsis; *Streptococcus pyogenes*.

Group A *Streptococcus* (GAS) is a Gram-positive bacterium that is a common infective pathogen in both children and adults [1]. It causes a wide spectrum of clinical disease, from common superficial illness, such as pharyngitis and pyoderma, to less common but serious invasive disease, such as bacteremia, necrotizing fasciitis, and osteomyelitis [2, 3]. Invasive GAS disease can be complicated also by toxin-mediated streptococcal toxic shock syndrome (STSS).

The incidence of invasive disease in high-income countries, where population-based data are most reliable, is fairly consistent at 3 to 5 cases per 100 000 per year, and the associated case-fatality ratio is 10% to 15% [3–11]. This burden of disease is comparable with that of invasive meningococcal disease in Australia and United States before the introduction of meningococcal vaccination [12–14]. In Australia, invasive GAS disease requires reporting in only 2 of its 8 jurisdictions, Queensland and the Northern Territory [15, 16].

In the developing world, the incidence of invasive GAS disease seems to be considerably higher, with an incidence between 10 and 43 per 100 000 per year, as observed in three different population-based studies (in Fiji, Kenya, and New Caledonia), and an associated case-fatality ratio in one study as high as 31% [17–19]. The incidence among indigenous populations in high-income countries has been reported to be up to 7 times greater than that among the rest of the population [20–22]. Among some indigenous groups, the excess burden of invasive GAS disease can be attributed to skin and soft-tissue infections as the primary source of infection [18].

The incidence of invasive GAS disease is highest at the two extremes of age in all settings. In a recent population-based study in Kenya, the rate of invasive GAS disease in neonates was 0.6 per 1000 live births [19], which is comparable to the rate of invasive group B *Streptococcus* disease in the United States and Australia [23]. Pediatric invasive GAS disease has been well

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studied in a number of high-income countries and was found to have an incidence of less than 6 per 100 000 in children. For example, in a population-based study in Australia, the incidence of invasive GAS disease peaked at 5 per 100 000 children aged less than 1 year and declined below that for children older than 5 years, similar to data from the most recent population-based study in the United States, in which a peak incidence of 5.3 per 100 000 infants younger than 1 year was found [6, 24]. In a recent nationwide pediatric surveillance study in Finland, the incidence in children aged less than 15 years was 2.5 per 100 000 per year, and the case-fatality ratio was 2% [25].

No vaccine against GAS is currently available, although attempts have been made over nearly a century to produce one, and at present, vaccines are in phase I and II clinical trials [26, 27]. Most vaccine candidates focus on the M protein, a surface protein that forms the basis for classifying GAS infections into different *emm* types [27]. More than 230 known *emm* types are known, and more continue to be identified [28–30]. Across high-income countries, the majority of GAS infections are the result of several predominant *emm* types, namely, *emm1*, *emm3*, *emm28*, *emm12*, *emm11*, and *emm4* [6, 27, 31]. Knowledge of the molecular epidemiology for a region is important for predicting the likely associated vaccine coverage [29], although a degree of cross-reactive immunity might increase vaccine coverage [18, 32].

A better understanding of the clinical presentation of children with invasive GAS disease, including their severity of illness, is required to inform clinical algorithms to improve disease recognition and patient management. These data are needed also to inform public health policy, including future evaluations of vaccine efficacy and cost-effectiveness.

METHODS

Study Design and Setting

Data were collected prospectively through active surveillance of patients with invasive GAS disease at the Royal Children's Hospital Melbourne between October 2014 and September 2016. The Royal Children's Hospital is the largest children's hospital in Australia; its has more than 330 beds and is one of two tertiary centers that service the state of Victoria [33]. The population of Victoria was 5.9 million people in 2016, and 18.3% were younger than 15 years [34]. Surveillance was performed using methodology developed by the Paediatric Active Enhanced Disease Surveillance (PAEDS) project, a nationwide initiative that enables hospital-based surveillance of serious but uncommon diseases [35]. This single-center study was intended as a pilot study before expansion to nationwide surveillance.

Case Definition

Patients were eligible for enrollment if they were younger than 18 years and admitted to the hospital with laboratory-confirmed invasive GAS disease, defined as the isolation of GAS from a normally sterile site, including blood, pleural fluid, and synovial fluid. STSS was defined using previously published criteria [36].

Classification

Patients were categorized according to their disease severity. Patients with severe disease were defined as those who required inotropic support or intubation with mechanical ventilation, whereas patients with very severe disease were those who required extracorporeal membrane oxygenation (ECMO). The emergency department triage classification, in accordance with the nationwide Australasian Triage Scale [37], has 5 levels of acuity; category 1 is reserved for disease that is immediately life-threatening, category 2, imminently life-threatening, category 3, potentially life-threatening, category 4, potentially serious, and category 5, less urgent.

Recruitment Protocol and Data Collection

After the identification of a GAS-positive isolate from a sterile site, the microbiology laboratory notified the research nurse. Once the case definition was confirmed, the patient and his or her family were approached for study recruitment. Comprehensive clinical details, including presenting features, triage category, and management information, were collected by completing a data-collection form entered into REDCap [38]. Data on disease presentation, severity, and outcomes and on the number and timing of preceding clinic presentations were extracted from the electronic medical record, and some clarification was obtained directly from medical personnel. In the event that an eligible patient was identified after discharge from the hospital, that patient's family was contacted by telephone, and an information statement was sent.

Follow-Up Data

A follow-up questionnaire was administered for all enrolled patients, by either telephone or e-mail, 6 months after discharge from the hospital. The families were asked about their child's readmissions and outpatient appointments and whether their child had ongoing health concerns and, if present, their nature. Motor function was evaluated by questions about the child's ability to complete day-to-day activities, mental status by questions about mood, behavior and concentration, sensory function by questions about sensitivity to touch, light, and temperature, and communication by questions about listening, talking, and writing.

Laboratory Procedures

All GAS isolates were sent to the Group A Streptococcal Research Laboratory at the Murdoch Children's Research Institute for *emm* typing using the protocol described by the Centers for Disease Control and Prevention [39], with some modifications described previously [40].

Data Analysis

Data were exported from REDCap into Stata 14.0 (StataCorp, College Station, Texas). Categorical data are presented as proportions and continuous data as means or medians. To compare between patients with severe disease and those with nonsevere disease, we used the Fischer exact test for comparison of proportions, and for continuous data, we used the t test and the Wilcoxon signed-rank test for normally and nonnormally distributed data, as appropriate.

RESULTS

The microbiology laboratory flagged 33 patients, and all of them were recruited into the study. Five patients were excluded from the analysis because their disease did not fulfill the case definition because the GAS isolate was not obtained from a truly sterile site (ie, fluid from upper airway sinuses, a superficial skin swab, bronchoalveolar lavage fluid, a thigh abscess, and a retropharyngeal abscess), which left 28 GAS cases for analysis (Table 1). Ten (36%) children were classified as having severe disease; 5 (18%) of these children fulfilled the criteria for STSS, and 2 (7%) met the criteria for very severe disease.

The median hospital length of stay in an acute inpatient bed was 8 days (range, 2–59 days). The median length of stay was longer for patients with severe disease (median, 14 days [range, 7–59 days]) than for those with nonsevere disease (median, 4.5 days [range, 2–28 days]) ($P = .004$). Seven children had an admission to the hospital in the home unit (a service that provides care to admitted patients with minimal care requirements in their home; they are considered to be inpatients and remain under the care of an overseeing physician). These admissions were mainly for intravenous antibiotic therapy, and the median length of stay in this service was 8 days (range, 3–44 days); 5 of these patients had osteoarticular infection. Two children were admitted for inpatient rehabilitation (for 10 and 74 days).

Clinical Syndromes and Microbiological Sites of Infection

Bacteremia without a clinical focus for infection was the most common presentation (n = 10 [36%]). There were 7

Table 1. Characteristics of 28 Children With Invasive GAS Disease

Characteristic	All Patients (n = 28)	Patients With Severe Disease (n = 10)	Patients With Nonsevere Disease (n = 18)	*P*
Age (mean [SD])	4.4 (2.8)	3.6 (2.5)	4.8 (3.0)	.15
Sex, male (n [%])	14 (50)	8 (80)	6 (33)	.023
Preceding risk factors (n [%])	19 (68)	7 (70)	12 (67)	.60
Pyoderma within 1 mo	1 (4)	1 (10)	0 (0)	.36
NSAIDS within 1 wk	15 (54)	4 (40)	11 (61)	.25
Comorbidities	7 (25)	4 (40)	3 (17)	.13
Underlying conditions (n [%])	7 (25)	4 (40)	3 (17)	.13
Eczema	3 (11)	2 (20)	1 (6)	.28
Congenital syndrome	1 (4)	0 (0)	1 (6)	.64
Neurofibromatosis	1 (4)	0 (0)	1 (6)	.64
Metabolic disorder	1 (4)	1 (10)	0 (0)	.36
Cirrhosis and liver failure	1 (4)	1 (10)	0 (0)	.36
Presenting symptoms				
Fever (n [%])	27 (96)	10 (100)	17 (94)	.64
No. of days (mean [SD])	3.2 (2.4)	2.6 (1.8)	3.6 (2.6)	.15
Limb pain (n [%])	16 (57)	5 (50)	11 (61)	.43
Lower limbs only	7 (44)	1 (10)	6 (55)	.18
Upper and lower limbs	9 (56)	4 (40)	5 (46)	.40
Inability to walk (n [%])	15 (54)	6 (60)	9 (50)	.46
Pain (aside from limb) (n [%])	7 (25)	2 (20)	5 (28)	.51
Lethargy or irritability (n [%])	17 (61)	6 (60)	11 (61)	.63
Vomiting and/or diarrhea (n [%])	10 (36)	7 (70)	3 (17)	.008
Presenting sign				
Fever (n [%])	22 (79)	8 (80)	14 (78)	.64
Maximum temperature in first 24 hours (mean [SD]) (°C)	39 (0.7)	39.0 (0.4)	39.0 (0.9)	.43
Rash (n [%])	12 (43)	6 (60)	6 (33)	.17
Hypotension (n [%])	5 (18)	4 (40)	1 (6)	.041
Initial WCC (mean [SD]) ($\times 10^9$/L)	16.2 (8.0)	14.1 (10.1)	17.3 (6.5)	.16
Initial CRP level (median [25th–75th percentile])[a]	164.5 (44–270)	248.5 (127–270)	160.5 (44–247)	.38
Initial procalcitonin level (median [25th–75th percentile])[b]	23.1 (20.5–155.6)	23.1 (20.5–155.6)	—	—

Abbreviations: CRP, C-reactive protein; GAS, group A *Streptococcus*; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; WCC, white blood cell count.

[a]Not all patients had a CRP level assessed. Results were available for: all (n = 22), severe (n = 4), nonsevere (n = 18), for values of CRP recorded as >270 these were changed to 270 for ease of analysis.

[b]Not all patients had a procalcitonin level assessed, results were available for: all and severe (n = 8).

different clinical foci of infection among the remaining 18 patients (Table 2). Twenty (71%) patients had positive blood culture results.

Predictors of Disease Severity at Presentation

The cases of 15 (54%) patients were reviewed by a medical practitioner, but then the patients were discharged, during in the 48-hour period preceding their eventual admission, either in the emergency department or in an outpatient setting. Seven of these patients had severe disease, including both patients with very severe disease, whereas 8 patients had nonsevere disease. Data for the first presentation of these 15 patients were not uniformly available. At admission, these patients tended to have more severe disease than those admitted at first presentation (47% vs 23%, respectively; $P = .10$), and more of them were admitted to intensive care (53% vs 38%, respectively; $P = .34$). Clinically, these patients were more likely to have upper and lower limb pain (70% vs 33%, respectively; $P = .09$) and rash (60% vs 23%, respectively; $P = .06$) and a higher initial mean white blood cell count ($P = .05$) and C-reactive protein level ($P = .026$) (Supplementary Table 1).

Lethargy was a common presenting complaint (17 patients) and occurred equally in patients with severe disease and those with nonsevere disease (Table 1). Gastrointestinal upset occurred in 7 patients with severe disease and in only 3 patients with nonsevere disease ($P = .008$), and hypotension was observed in 4 patients with severe disease and only 1 patient with nonsevere disease ($P = .04$). The presence of rash was observed more frequently among the patients with severe disease ($P = .17$, not statistically significant). Patients with severe disease were more likely to have a neutrophil count in the low-normal range than were those with nonsevere disease ($P = .049$) (Supplementary Table 2), and they were also noted to have thrombocytopenia ($P = .40$), hypoalbuminemia ($P = .001$), coagulopathy, and an elevated international normalized ratio ($P = .019$).

We found an overall expected association between emergency department triage category and disease severity. Only one patient with severe disease was categorized as category 3. All patients with severe disease received initial fluid resuscitation with at least 20 ml/kg on presentation. In comparison, 8 (44%) of the patients with nonsevere disease required fluid resuscitation boluses of up to 20 ml/kg.

Table 2. Clinical Syndromes Compared With Microbiological Sites of Infection

		Microbiological Site of Infection	
Clinical Syndrome	Total (n [%])	Blood (n [%])	Other (n [specify])
Bacteremia without focus	10 (36)	10 (36)	—
Pneumonia	6 (21)	2 (7)	4 (pleural fluid)
Osteoarticular	5 (18)[a]	4 (14)[a]	2 (joint fluid)
Cellulitis (including non-NF soft tissue)	5 (18)[a]	5 (18)[a]	—
Necrotizing fasciitis	1 (4)	1 (4)	—
Peritonitis	1 (4)	—	1 (peritoneal fluid)
Retropharyngeal abscess	1 (4)	—	1 (lymph node specimen)
Mastoiditis	1 (4)	—	1 (mastoid fluid)
All patients	28	20 (71)	9 (32)

Abbreviation: NF, necrotizing fasciitis.

[a]Two patients had multifocal infection and were included in >1 category.

Patients With Severe Disease

Thirteen patients were admitted to the intensive care unit. More boys had severe disease than did girls ($P = .023$) (Table 1). The median length of stay in intensive care was 6 days (range, 1–31 days). Six patients admitted to intensive care were transferred from another hospital by the emergency retrieval team, and 4 patients were admitted through the emergency department (1 with category 2 disease and 3 with category 3 disease). Ten patients required cardiorespiratory support; 9 (32% of all patients) children required intubation and mechanical ventilation (median duration, 5 days [range, 1–13 days]), and 9 children required inotropic support (median duration, 3 days [range, 1–11 days]). Two patients with very severe disease had a prolonged intensive care admission that required 5 and 7 days of ECMO. Both patients required prolonged inotropic support for 11 and 9 days and additional vasopressor support for 2 and 4 days and hemofiltration for 5 and 22 days, respectively. Both patients received intravenous immunoglobulin and corticosteroids and required multiple surgical interventions. Of all patients in our series, 17 required some form of surgical intervention ranging from limb amputation (n = 2), exploratory laparotomy (n = 2), fasciotomy (n = 1), joint washouts (n = 4), sternotomy for ECMO cannulation and cannula repositioning (n = 2), video-assisted thoracic surgery with chest drain insertion (n = 3), surgical drainage of deep abscess (n = 2), and line insertions and removals (n = 7), among others.

Duration of Treatment

Antibiotic treatment durations varied substantially depending on clinical disease manifestation and severity (Table 3). The median total duration of antibiotic treatment was longer for patients with severe disease (23.5 days) than for those with nonsevere disease (14.5 days) ($P = .16$); a similar difference between the 2 disease-severity groups was observed also for parenteral treatment (15 and 6 days, respectively; $P = .025$). The longest antibiotic treatment duration (72 days, parenteral; 76 days total) was for an 11-year-old patient with nonsevere disease for whom the diagnosis and treatment of osteoarticular invasive GAS disease were delayed. Six (21%) patients received adjunct treatment with both intravenous immunoglobulin and corticosteroids, and another 3 (10%) patients received only corticosteroids.

Contact Prophylaxis

The family contacts of 17 (61%) patients (6 patients with severe disease) were offered contact prophylaxis. Of the 4 patients

Table 3. Antibiotic Treatment Duration According to Clinical Disease Syndrome

		Duration of Antibiotics (days)					
		Intravenous		Oral		Total	
Clinical Syndrome	N	Median (Total)	Range	Median (Total)	Range	Median (Total)	Range
Bacteremia	10	5.5	3–18	7	0–14	14	8–18
Pneumonia	6	7.5	3–17	4.5	0–30	10.5	8–47
Osteoarticular	5	18	8–72	7	0–14	31	18–76
Cellulitis	3	10	2–25	10	10–14	20	16–35
Necrotizing fasciitis	1	(37)	—	(0)	—	(37)	—
Peritonitis	1	(20)	—	(7)	—	(27)	—
Retropharyngeal abscess	1	(16)	—	(22)	—	(38)	—
Mastoiditis	1	(5)	—	(10)	—	(15)	—
Total	28	8	2–72	7	0–30	16.5	8–76

whose families had not been offered prophylaxis, 2 were siblings. Twelve days after the index patient was admitted for invasive GAS disease complicated by STSS, the patient's sibling presented interstate with GAS empyema caused by the same *emm* type (*emm1*). The child was subsequently transferred to Victoria while the index patient remained in the intensive care unit at the time. There was an additional sibling pair among our study sample. The index patient was admitted with severe invasive GAS disease complicated by STSS. The following day, the patient's sibling was admitted and treated for scarlet fever, having a throat swab positive for GAS with the same *emm* type (*emm1*).

emm Types and Disease Occurrence

Among the 26 available isolates, we found 9 different *emm* types; 2 isolates were nontypeable (Figure 1). The most common *emm* type was *emm1* (n = 8 [31%]), which was also the most identified in patients with severe disease (n = 4 [44%]). Invasive GAS disease occurred most frequently between September and December (n = 15 [54%]), including the majority of *emm1* cases (n = 6); the remaining *emm1* cases (n = 2) occurred between July and September.

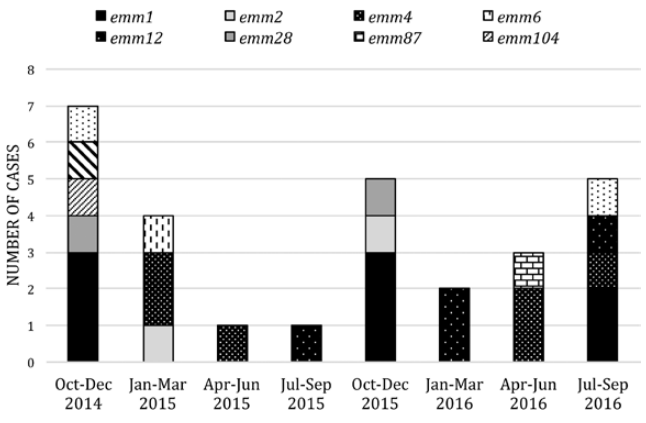

Figure 1. Distribution of emm types isolated from patients with invasive group A Streptococcus disease, October 2014 to September 2016.

Outcomes and 6-Month Follow-Up Assessment

No deaths in this study. Data on follow-up 6 months after presentation were available for all the patients. Eighteen (64%) patients had at least 1 outpatient follow-up appointment after discharge. Nine (32%) patients had ongoing health issues, as reported by their family, 6 (21%) directly related to invasive GAS disease. Five (18%) children had ongoing motor impairment, of whom, 2 (7%) children had a major physical disability as a consequence of invasive GAS disease (bilateral below-knee amputation and severe avascular necrosis of the hip). Four (14%) children experienced mild impairment of mental status, another 4 children experienced mild impairment of communication, and 1 (4%) child experienced mild impairment of sensory function. Five (18%) children had been readmitted subsequent to their admission episode for invasive GAS disease.

DISCUSSION

Invasive GAS disease in children in our study was frequently severe; 36% of our cohort required cardiorespiratory support. Although no deaths occurred among our study population, the long-term morbidity was considerable; at least one-fifth of these patients experienced ongoing medical problems because of their invasive GAS disease 6 months after discharge. We found a wide spectrum of clinical disease manifestations, comparable to that in previously published reports on studies of pediatric cohorts [25].

At our study site, 28 children with invasive GAS disease were admitted during the study period, compared with 14 children with invasive meningococcal disease during the same period (Nigel Crawford and Jim Buttery, unpublished data). A need exists for increasing public health and population awareness of invasive GAS disease, and vaccine development against GAS must be accelerated for a longer-term public health effect.

The very high proportion of patients treated and discharged before presentation in our study (n = 15 [54%]) was far higher than we expected, especially for those with severe disease (n = 7 [70%]).

Our study was not designed to investigate whether there are possible clinical or biochemical "red flags" suggestive of invasive GAS disease at initial presentation, whether there might be a window for earlier diagnosis, and, if so, whether there is a need for additional research into early diagnostic methods and warning signs for invasive GAS disease.

emm1 was the most frequent *emm* type observed in this study, which is consistent with data from other high-income countries and from Victoria, where it has been attributed to cause up to 24% of invasive disease [6, 24, 25, 29, 41]. We identified 4 of the 6 previously described most common *emm* types in high-income countries (*emm1*, *emm4*, *emm12*, and *emm28*), which accounted for disease in 20 (76%) of our patients.

Most published reports of invasive GAS disease from temperate countries, including that of a pediatric study in Finland, observed a peak incidence in winter and early spring [4, 6, 25]. A review of US surveillance data over the past 10 years found a variance in seasonality according to *emm* cluster [18, 42]; AC clusters, inclusive of *emm1*, tended toward winter months, and E clusters tended toward summer months [43]. In contrast, in our study, we observed a peak in incidence in late spring and early summer, with a predominance of *emm1* cases also occurring during this time period. Although our data set was small, this observation occurred over 2 years; therefore, additional large-scale population studies are required to draw more firm conclusions.

There were 2 main limitations to our study. First, ours was a single-center study, which is likely to have caused ascertainment bias, and it is possible that we overestimated disease severity because the most unwell patients are admitted to the Royal Children's Hospital. Furthermore, performing a single-center study meant that we could not estimate the population-based incidence. Second, we used a strict case definition for invasive GAS disease. By including only patients with microbiologically proven infection from a sterile site, we excluded patients with probable invasive GAS disease. We were aware of at least 4 patients who would have met the criteria for "probable" disease using previous case definitions [17]. Although our strict case definition resulted in limitations, our methodology is reproducible and can be implemented easily as a laboratory-based surveillance system to produce reliable minimum estimates of disease burden. In this study, we accepted a small but significant underrepresentation of overall disease burden for the sake of having a simple surveillance system. If greater resources are available for future studies, we would advocate for the inclusion of patients with probable disease after careful clinical review.

The success of surveillance in our study has enabled establishment of this system at 6 additional pediatric centers across Australia using the PAEDS network [35]. Increased public health and population awareness of invasive GAS disease is needed. Also, vaccine development against GAS must be accelerated for a longer-term public health effect. As research into GAS vaccines progresses, documentation of the incidence, severity, outcomes, and *emm*-type distributions of invasive GAS disease is important for informing vaccine development, future vaccine-efficacy studies, and advocacy efforts.

Supplementary Data

Supplementary materials are available at *Journal of the Pediatric Infectious Diseases Society* online.

Notes

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