Invasive Group A Streptococcal Disease in Children and Association With Varicella-Zoster Virus Infection

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ABSTRACT. *Objectives.* **To describe the incidence and clinical features of invasive group A streptococcal (GAS) disease in children in Ontario and determine the risk of invasive GAS infection following chickenpox.**

Methods. **During 1992–1996, we conducted prospective, active, population-based surveillance for pediatric invasive GAS disease in Ontario, Canada (population: 11 million; 2.5 million children) and reviewed clinical and laboratory records.**

Results. **There were 1.9 cases of invasive GAS disease per 100 000 children per year. Streptococcal toxic shock syndrome (STSS) occurred in 7% of cases and necrotizing fasciitis (NF) in 4% for incidences of .08 and .13 per 100 000 per year, respectively. Case-fatality rates were 56% for STSS, 10% for NF, and 4% overall. The presence of chronic underlying illness other than asthma was associated with death (relative risk [RR]: 11; 95% confidence interval [CI]: 2.4–45). Fifteen percent of children identified had preceding chickenpox infection, which significantly increased the risk for acquisition of invasive GAS disease (RR: 58; 95% CI: 40–85). Children with invasive GAS and recent chickenpox were more likely to have NF (RR: 6.3; 95% CI: 1.8–22.3).**

Conclusions. **Childhood invasive GAS disease occurs at an incidence similar to the adult population but has a lower rate of STSS and case-fatality. Chickenpox dramatically increases the risk for acquiring invasive GAS disease, and universal chickenpox vaccination could potentially prevent up to 15% of all pediatric invasive GAS disease.** *Pediatrics* **2000;105(5). URL: http://www.pediatrics.org/cgi/content/full/105/5/e60;** ***varicella, group A streptococcus, pediatric, risk.***

ABBREVIATIONS. GAS, group A streptococcus/streptococcal; NF, necrotizing fasciitis; STSS, streptococcal toxic shock syndrome; VZV, varicella-zoster virus; RR, relative risk; CI, confidence interval; IL, interleukin.

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A list of the members of the Ontario Group A Streptococcal Study Group appears in the "Appendix."

Received for publication Oct 5, 1999; accepted Dec 20, 1999.

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The past 15 years have witnessed a striking resurgence in the incidence and severity of infections caused by group A streptococci (GAS), including necrotizing fasciitis (NF) and the streptococcal toxic shock syndrome (STSS).[1–9] Numerous hospital-based case series have been reported on the clinical spectrum of pediatric invasive GAS disease and have identified that varicella-zoster virus (VZV) infection commonly precedes these infections, especially in cases of NF.[10–21] However, to adequately define the epidemiology of these infections, population-based studies are required. Published reports from population-based surveillance of invasive GAS infection have included relatively few pediatric cases.[3,5] This limits conclusions regarding the incidence and clinical features of this disease in children.

Our group previously reported the results of prospective, population-based surveillance for invasive GAS disease in Ontario, Canada, in 1992–1993, identifying 323 cases of which only 81 were in children.[3] The objective of this study was to describe the incidence and clinical features of invasive GAS disease in children in a large population (Ontario) and to better quantify the risk of this disease following chickenpox infection.

METHODS

Patient Population and Definitions

Prospective surveillance of invasive GAS infection on all residents of Ontario, Canada (population: 11 million; 2.5 million <18 years of age) was performed from January 1, 1992 to December 31, 1996. Invasive GAS infection was defined as disease associated with the isolation of *Streptococcus pyogenes* from a normally sterile body site. Patients were considered to have STSS if they met the consensus definition of the Working Group on Severe Streptococcal Infections.[22] Children who were dead on arrival at an emergency department or who died during resuscitation attempts without sufficient laboratory test results available to meet criteria for STSS were also considered to have STSS. NF was diagnosed using the criteria of Kaul et al.[2] Cases were considered nosocomial if the disease was not present or incubating at the time of admission.[23] The varicella vaccine was not introduced in Canada until December 1998, and no studies of varicella vaccines were performed in Canada before the date of licensure.

Study Protocol

All 155 microbiology laboratories serving hospitals and emergency departments and the 2 largest reference laboratories serving >75% of physicians' offices in Ontario reported all cases in which GAS was isolated from a sterile site. Cases were screened to confirm that the patient was a resident of Ontario, and then, clinical data on age, gender, risk factors, clinical disease, and outcome were collected from the patient's physician or by the

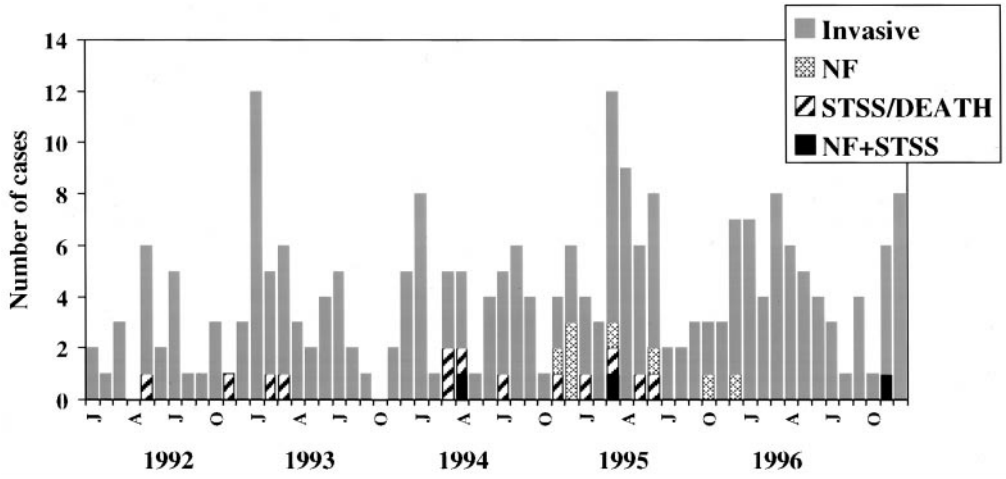

Fig 1. Occurrence of invasive disease attributable to GAS in children: Ontario, Canada, 1992–1996. The number of new cases of invasive GAS infection is shown by month (J indicates January; A, April; J, July; O; October).

hospital infection control practitioner using a standard data collection form. Some of this information was obtained directly from health records (eg, underlying diseases such as leukemia and use of steroids), whereas some involved direct questioning of patients (eg, history of nonsteroidal antiinflammatory use). Annual audits of laboratory records were performed to evaluate reporting accuracy and to identify cases not originally reported. The study was approved by the Human Subjects Review Committee of the University of Toronto.

Calculation of Incidence Rates, Relative Risk (RR), and Estimates of Vaccine Efficacy

Incidence rates were calculated using population statistics from Statistics Canada.[24] The attack rate associated with cases of chickenpox for children under 10 years of age was calculated using the number of cases complicating an acute attack of chickenpox (within the preceding month) as the numerator and estimating the denominator (the number of cases of chickenpox over the 5-year period) by assuming that 85% of the population is affected by 10 years of age, that the incidence is constant over time, and that 95% of infections are associated with skin lesions.[3,25] In calculating the RR of developing GAS infection in association with chickenpox, it was assumed that the risk associated with chickenpox is present for 2 weeks after the onset of lesions. Population estimates of the prevalence of asthma were obtained from the Ontario Health Survey.[26] The prevalence of acute leukemia was estimated using Canadian leukemia incidence rates for cohorts of children 0 to 4, 5 to 9, and 10 to 14 years of age and by assuming an 80% survival rate for each cohort.[27]

Microbiology

Clinical isolates were sent to the study laboratory and confirmed as GAS using standard techniques. M-protein typing was performed at the National Center for Streptococcus (Edmonton, Canada).[28–30] The presence of *spe*A and *spe*C genes was assessed using polymerase chain reaction.[31]

Statistical Analysis

Statistical analysis was performed using Statistica, Version 5.0 computer software program (StatSoft, Inc, Tulsa, OK), and SAS, Version 6.12 (SAS Institute, Cary, NC). Group proportions were compared using Fisher's exact test. Group means were compared using Student's t test. A multivariable logistic regression model was developed to test the association between the predictor variables of demographics (age and sex), clinical syndrome, microbiology (type of culture-positive, M serotype, and toxin genotype), and the outcome variables of NF or death. Differences in incidence were assessed using a normal approximation for the comparison of Poisson counts.[32]

RESULTS

Incidence and Demographics

During the 5 years of surveillance, 1087 cases of invasive GAS disease were identified in residents of Ontario; 243 (22.4%) of these occurred in children. Detailed clinical information was available for 211 (87%) pediatric cases. The incidences of NF and STSS were .08 and .13 per 100 000 children per year, respectively. The overall incidence of disease in children was 1.9 per 100 000 population per year, varying from a low of 1.1 per 100 000 in 1992 to a high of 2.3 in 1995 (Fig 1). Sixty-one percent of cases occurred from November to April ($P < .01$), compared with May to October. The incidence was higher in males (2.1/100 000 per year, compared with 1.6/100 000 in females; $P = .05$). The median age of patients was 5.4 years old (range: 0 days to 17 years), and the incidence of disease decreased with increasing age with a plateau between 1 and 9 years of age (Fig 2). There were 3 cases of early-onset neonatal sepsis (occurring in the first week of life), for a rate of .13 per 100 000 live births, and 5 additional cases occurred during the first 90 days of life.

Clinical Syndromes

A wide variety of clinical syndromes were associated with invasive GAS disease (Table 1). Cellulitis, upper respiratory infection, and bacteremia without focus were the most common syndromes. Osteomy-

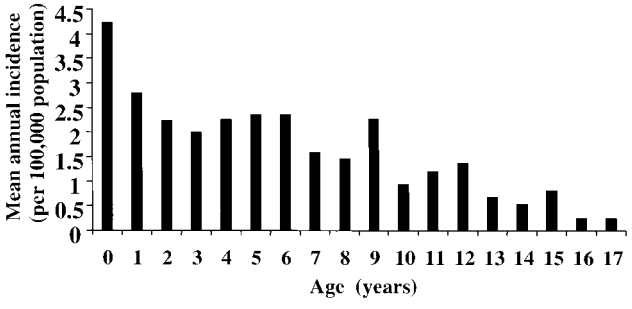

Fig 2. Age-specific incidence of invasive GAS disease in children: Ontario, Canada, 1992–1996.

TABLE 1. Clinical Syndromes Associated With Pediatric Invasive Group A Streptococcal Infection: Ontario, Canada, 1992–1996

Clinical Syndrome*	Total (N = 243)†
Cellulitis‡	74 (30%)
Necrotizing fasciitis§	10 (4%)
Upper respiratory‖	45 (18%)
Bacteremia without focus	39 (16%)
Arthritis¶	33 (14%)
Adenitis#	25 (10%)
Pneumonia	15 (6%)
Osteomyelitis**	12 (5%)
Abdominal††	10 (4%)
Meningitis	5 (2%)
Endocarditis	2 (.8%)
Septic iliac vein thrombosis	1 (.4%)

* All the clinical syndromes were accompanied by isolation of GAS from a normally sterile site, such as blood, bone, cerebrospinal fluid, etc.
† Numbers in columns exceed number of patients because 27 (11%) patients had more than 1 syndrome.
‡ Site of infection was specified for 57/74 patients: 16 lower limb, 10 upper limb, 11 trunk, 11 periorbital, 8 other head/neck, and 1 multiple.
§ Site of infection was leg in 3 patients, thigh in 5, and hand and abdominal wall in 1 each.
‖ Site of infection was specified for 34/45 patients: 11 pharyngitis, 5 tonsillitis/tonsillar abscess, 5 otitis media, 5 sinusitis, 5 retropharyngeal abscess, 1 parotitis, 1 pharyngitis and otitis, and 1 tracheitis.
¶ Joints involved were specified for all 33 patients: 10 hip, 8 knee, 5 ankle, 3 elbow, 2 shoulder, 1 hip and elbow, 1 hip and knee, 1 elbow, ankle and knee, 1 sacroiliac, and 1 first metatarsophalangeal.
# Lymph node sites involved were available for 23/25 patients and included: 17 cervical, 3 groin, 2 axillary, and 1 submental.
** Bones involved were available in 10/12 cases and included: 4 tibia, 1 each calcaneous, femur, humerus, patella, and 2 multifocal.
†† Cases included 5 peritonitis, 2 appendicitis, 1 perirectal abscess, and 1 late infection in which previously implanted mesh fistulized to small bowel.

elitis occurred only in children <10 years of age (P = .13). Lymphadenitis was more likely to occur in children under 10 years of age (23/194 vs 4/48; P = .06), whereas other soft tissue infections (cellulitis and NF) occurred more commonly in children 10 years of age and older (60/194 vs 44/48; P = .02). Ten children (4%) had NF, 3 of whom had STSS. In contrast to cellulitis, which was distributed across all body sites, 8 of 10 cases of NF occurred in the lower limb (P = .001), and 5 of 8 of these initially involved the thigh and/or groin.

Sixteen episodes of illness (7%) were classified as STSS: 6 with bacteremia without focus, 3 with NF (1 with concomitant pneumonia), 2 others with pneumonia (1 with cellulitis and 1 with peritonitis), 2 with cellulitis, and 1 each with pharyngitis and an infected iliac vein thrombus. Children under 10 years of age were less likely to be diagnosed with STSS than children 10 years of age and older (8/194 vs 4/48; P = .002).

Eighteen (7%) GAS infections were acquired either nosocomially or in relation to invasive procedures. These included 2 deep surgical site infections (1 abscess post appendectomy and 1 arthritis post arthroscopy), 7 superficial surgical site infections, 5 intravascular device-related bacteremias (3 implanted ports and 1 central and 1 peripheral intravenous line), 1 nosocomial primary bacteremia, 1 early neonatal pneumonia in an infant whose mother had GAS endometritis, and 1 infection each occurring after a childhood vaccination and the repair of a scalp laceration.

Underlying Conditions/Risk Factors

Thirty-eight (16%) children with invasive GAS had at least 1 chronic underlying illness (Table 2). In 3 of these children (1% of all cases), a diagnosis of malignancy (2 acute leukemia and 1 neuroblastoma) was made when the child presented with invasive GAS infection. A total of 6 children had a diagnosis of leukemia, with an estimated RR of invasive GAS infection in children with leukemia compared with other children of 44 (95% confidence interval [CI]: 30–56). In contrast, children with asthma were not more likely than were others to develop invasive disease (RR: .74; 95% CI: .42–1.33). Children with chronic underlying illnesses accounted for 5 of 17 (29%) cases of nosocomial or iatrogenic disease.

Thirty-one children (15% of 205 for whom data were available) had a history of chickenpox during the month before their illness. All chickenpox-associated cases occurred in children under 10 years of age. Invasive GAS infection was diagnosed a median of 5 days (range: 4–12 days) after the onset of VZV rash. Of the 31 patients, 13 had cellulitis, 5 NF (2 with concomitant pneumonia), 4 arthritis, 3 bacteremia without focus, and 1 each pharyngitis, parotitis, axillary adenitis, peritonitis, osteomyelitis, and endocarditis. The attack rate for invasive GAS disease in children in the 2 weeks after chickenpox was 5.2 per

TABLE 2. Chronic Underlying Illness in Children With Invasive GAS Infection: Ontario, Canada, 1992–1996

Underlying Illness	Number of Cases (n = 211)*	Number (%) of Deaths (n = 9)	Number (%) With STSS (n = 10)*	Number (%) With Nosocomial/ Iatrogenic Disease (n = 17)
None	173	3 (2%)	7 (4%)	12 (7%)
Asthma	12	0	0	1 (8%)
Malignancy†	11	1 (9%)	0	4 (36%)
Congenital cardiac disease	4	1 (25%)	1 (25%)	0
Biliary atresia	3	1 (33%)	0	0
Other‡	8	3 (38%)	2 (25%)	0

* Data on underlying illness were available for 211 of 243 (87%) of cases.
† Comprise: 6 acute leukemia, 3 neuroblastoma, 1 sarcoma, and 1 astrocytoma.
‡ Other conditions included: 1 patient each with juvenile rheumatoid arthritis, dermatomyositis, renal transplant, seizure disorder, ependymoma of brainstem, quadriplegia, cerebral palsy with gastroparesis and malnutrition, and multiple congenital anomalies.

100 000, compared with .09 per 100 000 without chickenpox (RR: 58; 95% CI: 40–85). Only 1 of 20 chickenpox patients for whom medication histories were available had taken a nonsteroidal antiinflammatory agent during the previous week.

Children with invasive GAS infection who had recent chickenpox were more likely to have a soft tissue focus of infection (18/31 vs 11/174; RR: 2.4; 95% CI: 1.6–3.6; $P = .004$) and NF (5/31 vs 1/157; RR: 6.3; 95% CI: 1.8–22.3; $P = .007$). However, cases with and without chickenpox were not different in the rate of positive blood culture results (18/31 vs 114/174; $P = .9$), intensive care unit admission (2/26 vs 64/159; $P = .5$), STSS (1/31 vs 1/170; $P = 1.0$), or case fatality (1/31 vs 1/173; $P = 1.0$).

There was a history of recent trauma/skin breakdown recorded for 84 (41%) children for whom information was available. In addition to the 31 patients with chickenpox, there were 15 (7%) patients with nosocomial disease associated with wounds or intravenous sites; 27 (13%) other children with lesions, such as abrasions, burns, and body piercing; and 11 (5%) who had suffered blunt trauma before illness. Fifty-five percent (41/74) of children with soft tissue infection had open skin lesions, compared with 23% (31/132) of children with other diagnoses ($P < .0001$). Thirty-two children (15% of 215 for whom data were available) had had recent contact with either proven GAS pharyngitis (17 children), pharyngitis that was not cultured (12 children), or other GAS disease (3 cases of cellulitis).

Microbiology

In 158 of 243 cases (65%), GAS was isolated from blood cultures. In the 85 cases in which blood cultures were negative or not performed, isolates were obtained from tissue taken at surgery in 19, synovial fluid in 18, pleural fluid in 6, peritoneal fluid in 5, cerebrospinal fluid in 2, and aspirates of tissue or abscesses in 35.

Isolates were available for typing from 208/243 (86%) of all patients. The predominant M types were M1 (27%), M12 (15%), M4 (11%), M3 (10%), M28 (6%), M11 (4%), M6 (3%), and M22 (3%). Thirteen percent of isolates were M-nontypable. Sixty-three (30%) of isolates contained the gene for *spe*A, and 85 (40%) contained the gene for *spe*C. Neither M-type nor toxin genotypes were associated with clinical syndrome, presence of STSS, or death.

Outcomes

The overall case fatality rate was 4.1% (10/243). One patient (10%) with NF died at presentation to the emergency department. No other patients with NF alone or in combination with STSS died. Patients with STSS had a much higher case fatality rate of 56% (9/16) , compared with .5% (1/227) for others ($P < .0001$). This was also true if the analysis was limited only to cases fulfilling consensus criteria for STSS (3/11 vs 1/226; $P < .001$).[22] Of the 10 children who died, 3 were dead on arrival at hospital, 4 died during resuscitation attempts within 12 hours of arrival, 2 died 12 to 48 hours after admission, and 1 child died after 48 hours. The late death occurred in an infant with biliary atresia who died 16 days after admission for GAS sepsis attributable to a supervening sepsis with *Citrobacter spp*. For 3 children who died (including both children who died 12–48 hours after admission), an original diagnosis of bacterial infection was not made. One child who was dead on arrival had been seen by a physician ~16 hours before death and was thought to have viral gastroenteritis. Two children, who died 12 and 36 hours after admission, respectively, were diagnosed as having viral infections (meningitis and synovitis) and did not initially receive antibiotics.

The majority of children (233/243; 96%) were admitted to hospital. Twenty-eight (12%) required intensive care unit admission, and 19 (8%) mechanical ventilation. For survivors with community-acquired disease who did not have another diagnosis that extended length of stay, such as leukemia, the median length of stay was 7 days (range: 1–65 days). The median length of stay for 9 children surviving with NF was 20 days (range: 6–65 days). Of the 9 surviving children with NF, 1 required bilateral below knee amputations and the remaining 8 had 1 or more surgical procedures for debridement, with 2 requiring pedicle flap grafts for closure. Forty-six patients without NF underwent surgery ranging from appendectomy to sequestrectomy to soft tissue debridement. Fourteen patients with arthritis had joints drained, and 4 patients with pneumonia had chest tubes inserted for drainage of effusions or empyema. Eight patients required a second surgical procedure (7 soft tissue debridement and 1 muscle graft).

Factors Associated With Death and NF

The following factors were included in analyses of factors associated with death and with NF: age, sex, local site of infection at presentation, M serotype of infecting strain, and presence of underlying illness, varicella infection, and NF. In univariate analysis, children were more likely to die if they had a chronic underlying illness (6/38 vs 8/174; $P = .001$) or no evident focus of infection (6/38 vs 8/191; $P = .002$). The increased case fatality rate associated with chronic underlying illness was caused by conditions other than asthma, as no child with asthma died, compared with 6/24 (25%) of cases with other underlying illnesses ($P < .001$). In multivariate analysis, only the presence of chronic underlying illness was significantly associated with death (RR: 11; 95% CI: 2.4–45).

In univariate analysis, only the presence of antecedent chickenpox was associated with the diagnosis of NF (5/31 vs 4/157; RR: 6.3; 95% CI: 1.8–22.3; $P = .007$). In multivariable analysis, both in all cases and in the subset with soft tissue infections, only chickenpox was associated with the diagnosis of NF (for the subset of children with soft tissue infection, RR: 4.5; 95% CI: 1.0–20; $P = .04$).

DISCUSSION

The most striking finding of this study is the observation that VZV infection is associated with a 58-fold (95% CI: 40–85) increased risk of acquiring

invasive GAS disease in children. It is not clear why chickenpox infection increases the risk for GAS infection so dramatically. One possibility is that invasive disease occurs as a consequence of the increased rate of superficial skin infection caused by the chickenpox lesions causing breakdown in the skin barrier. This is supported in part by the observation that the majority of chickenpox-associated infections occurring in this study had a soft tissue focus. However, the risk of invasive GAS infection at sites not directly related to skin was also increased, which suggests that other mechanisms predisposing to invasive infection are important. VZV infection itself may cause a predisposing immune aberration or may allow invasion via another less apparent portal, such as lesions on the oral mucosa or the respiratory tract. In favor of an immune aberration is the fact that NF, the most severe manifestation of soft tissue infection, tended to occur more commonly in association with chickenpox than in nonchickenpox cases. Furthermore, Fujimara et al[33] have presented evidence of a switch of the $CD4^+$ T cell profile in patients with varicella and underlying atopic dermatitis from a T_{H2} to a T_{H1} dominant type with a relative immunosuppression. TH1 cells produce interferon-γ and interleukin 2 (IL-2) and promote cellular immunity, whereas TH2 cells produce IL-4, IL-5, IL-10, and IL-13 and promote humoral immunity.[34,35] The associated decrease in humoral immunity may be important in pathogenesis of a bacterial disease, such as invasive GAS infection.

Some investigators have suggested that nonsteroidal antiinflammatory drugs may increase the risk for GAS NF in children with chickenpox.[17,36,37] A recent case–control study suggested a link between ibuprofen use and NF in children with varicella.[36] However, most of the patients who used ibuprofen did so only after the onset of GAS symptoms and the use of this drug is likely to have been a response to infection in persons with severe disease rather than a cause. We observed a low (1/20) rate of nonsteroidal antiinflammatory drug use in children with chickenpox-associated invasive GAS infection in our study suggesting that these drugs did not play an important role in our patient population. Regardless of the mechanism, this study provides strong evidence that VZV infection predisposes children to invasive GAS infection and particularly NF.

One other group of investigators reported population-based data on the risk of invasive GAS disease associated with chickenpox. Zurawski et al[5] in a prospective population-based study in Atlanta calculated an annualized RR of 12.2 (95% CI: 5.6–26.6) associated with chickenpox infection. The difference in this rate from our estimate is in part attributable to differences in calculation and their smaller sample size (41 children under 10 years of age). We assumed, and our data supported, that the risk for invasive GAS infection is only increased for up to a 2-week period following chickenpox infection. Thus, using this assumption, the RR of invasive GAS infection for children resident in the metropolitan Atlanta study in association with chickenpox is 170 (95% CI: 90–322), somewhat higher than found in our study. This difference is mostly because the percentage of pediatric cases that were associated with acute varicella was considerably higher in Atlanta (37%) than in Ontario (16%) and in other published case series (median: 16%; range: 6%–29%).[10,11,13,16,19,38,39] The reason for the higher rate of varicella-associated cases in Atlanta is not clear but may be related in part to an increased varicella activity over a shorter period of observation (18 months). Because varicella vaccine was not available in Canada until 1998, use of chickenpox vaccine in our population could not have contributed to lower rates.

Although the attack rate for invasive GAS disease following chickenpox is relatively low at 5.2 per 100 000, it is important that 15% of all pediatric invasive GAS infection in this study, including 50% of NF cases, followed VZV infection. Because there is an effective, safe vaccine for chickenpox available, many cases of invasive GAS disease, including NF, may potentially be preventable by chickenpox vaccination of young children. We have estimated the impact of universal chickenpox vaccination effectiveness in preventing invasive GAS infection using the following assumptions: 1) vaccine coverage would be 80%, 2) vaccine efficacy for preventing chickenpox manifested by any skin lesions would be 85%, 3) vaccine would be administered at 1 year of age, and 4) the risk of invasive GAS infection would be equal in vaccinated and nonvaccinated children with skin lesions following wild type VZV infection.[40–45] Based on our data and these assumptions, we estimate that universal vaccination of 1-year-old children would prevent at least 10% of all invasive GAS infections. Given that our estimates of vaccine efficacy (85%) and coverage (80%) are conservative, the effect of vaccination is likely greater than 10%. These data lend further support to the arguments in favor of introducing VZV vaccination into the routine childhood regimen.[46,47]

There is general agreement among experts that invasive GAS disease has been increasing in incidence since the mid-1980s. However, there are no prospective population-based studies from that decade to directly compare with current incidence rates. This study shows that the rate of invasive GAS infections in the Ontario pediatric population doubled from 1992 to 1995. The number of cases seen at the Hospital for Sick Children in Toronto during this period (median: 7.5; range: 4–9 cases per year from 1992–1995) increased, compared with the 1985–1991 period (median: 3; range: 1–6 cases per year; $P = .03$; Wilcoxon rank sum) as identified from a previous retrospective study.[11] These data, although not conclusive of increased incidence, are compatible with results of population-based surveillance in Scandinavia and Israel and several North American hospital-based case series, which reported an increase in invasive GAS disease in both adults and children in the early 1990s.[6,9,10,12,16,21] Whether this increase represents a shift in the incidence of these infections that will be maintained or a peak in naturally variable incidence remains to be established.

This study confirms previous observations that the epidemiology and clinical features of invasive GAS

disease vary among age groups.[3,11] Younger children were more likely than older ones to have osteomyelitis, lymphadenitis, and chickenpox-associated disease but less likely to have STSS. We observed lower rates of STSS (7%) and case-fatality (4%) in children in the present study than we did for adults (STSS rate: 13%; overall case-fatality rate: 15%) in our previous report.[3] Adults have higher rates of underlying illnesses than children and differential rates of chronic disease likely provide much of the explanation for the differences in case-fatality rates between children and adults.[3] Underlying illness is an important predictor of outcome and was the only significant variable associated with death in multivariate analysis in children in this study (RR: 11; 95% CI: 2.4–45). It is important clinically to recognize this increased risk for death in these children with invasive GAS disease. In addition, a history of chickenpox and cellulitis on the lower extremities in children warrants a high index of suspicion for the diagnosis of NF. However, if interventions to reduce death rates from invasive GAS disease are possible, management early in the disease course appears to be necessary as nearly all (90%) of the deaths observed in this study occurred within 48 hours of presentation to hospital.

The M type distribution in the children in our study was different to that noted among 844 Ontario adults we identified with invasive GAS disease during the same period. Although M type 1 was most common, as in adults, there were more infections by M type 12 (15% vs 8%; $P < .01$) and M type 4 (11% vs 4%; $P < .01$) in children. However, similar to the situation in adults,[3] we did not find an association between M serotype and streptococcal toxic shock syndrome or death, suggesting other factors were contributory. We did not check the M type distribution of noninvasive GAS isolates during the study. This would have been useful to explain whether the increased rates of M types 12 and 4 in invasive disease in children simply reflected increased colonization by these 2 types.

CONCLUSION

In summary, although pediatric invasive GAS disease occurs at an incidence similar to that for adults, it has a much lower rate of STSS and case-fatality. The presence of underlying medical conditions other than asthma is important both as a risk factor for acquisition of invasive GAS disease and as a predictor for mortality. Chickenpox infection is the most important risk factor identified for the acquisition of invasive GAS infection in children. Vaccination of 1-year-old children with chickenpox vaccine would be expected to prevent at least 10% of all invasive GAS disease in children and the majority of NF. Its inclusion in the routine childhood vaccination schedule is recommended.

APPENDIX

The following are other members of the Ontario Group A Streptococcal Study Group: A. Fletcher, R. Kaul, and B. Willey (Mount Sinai and Princess Margaret Hospitals, Toronto, Canada); B. Demers (Institut Pasteur, Paris, France); M. Lovgren and J. Talbot (National Center for Streptococcus, Edmonton, Alberta, Canada); and M. Naus (Ontario Ministry of Health, Toronto, Canada).

ACKNOWLEDGMENTS

This work was supported in part by a contract from the Centers for Disease Control and Prevention (Atlanta, Georgia) and MDS Health Group (Toronto, Canada).

Dr Davies is supported through a Clinical Investigator Award of the Alberta Heritage Foundation for Medical Research, and Dr Low is supported in part by an award from the Canadian Bacterial Diseases Network.

We are indebted to the microbiology laboratories, infection control practitioners, and physicians across Ontario without whose time, effort, and enthusiasm this surveillance would not be possible; to the many staff of the Ontario Ministry of Health and public health departments across Ontario who have supported this study and assisted in investigations; and to Ruth Jaeger, Mark Jogersma, and Paul Grantham of MDS Health Group Limited for transport of specimens.

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Pediatrics 2000;105;e60
DOI: 10.1542/peds.105.5.e60

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