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BRIEF REPORT

Invasive Group A *Streptococcus* Infection in Children in Southern Israel Before and After the Introduction of Varicella Vaccine

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The annual rates of group A *Streptococcus* bacteremia per 100 000 children in southern Israel declined after introduction of the varicella vaccine to the national immunization program, from 2.43 (95% confidence interval, 1.73–3.13) in 1995–2002 to 1.30 (95% confidence interval, 0.91–1.72) in 2010–2016 (P = .04). This reduction correlated with the disappearance of varicella rash as a predisposing factor.

Keywords. *emm* type; invasive group A *Streptococcus*; varicella vaccine.

Dynamics of invasive group A *Streptococcus* (GAS) infection in children might be attributed to variations in bacterial virulence or predisposing host factors [1]. M protein, which is encoded by the *emm* gene, is a major GAS virulence factor. The predominant M-type proteins in circulation vary among different geographic regions, and they enter and leave communities unpredictably [2]. Skin lesions, including those that are associated with varicella, are a major risk factor for invasive GAS (iGAS) infection in children [3]. Other known risk factors are recent trauma and surgery.

The association between iGAS and varicella infection has been well described; pediatric varicella-related iGAS hospitalizations have declined, which is associated temporally with use of the varicella vaccine [4].

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The Pediatric Infectious Disease Unit at the Soroka University Medical Center (SUMC) conducted a population-based surveillance study of iGAS infections that began 13 years before introduction of the varicella vaccine and continued for 14 years after implementation.

The aims of the study were to (1) identify the dynamics of iGAS bloodstream infections (BSIs) before and after introduction of the varicella vaccine and (2) detect changes in clinical presentation, risk factors, and predominance of *emm* types in children with iGAS infection.

METHODS

Setting

Nearly all children born in the Negev region of Israel receive emergency and inpatient services at the SUMC, because it is the only hospital in the region. The pediatric population of the Negev region has been increasing steadily (from 187 800 in 1995 to 294 500 in 2016).

The varicella vaccine was introduced to the private market in 2003, resulting in vaccine coverage of <30%, and to the national immunization program (NIP) in September 2008 and is given as 2 doses at the ages of 1 and 6 to 7 years for children born after January 1, 2007, or in a catch-up program of 2 doses with a 6-week interval for children born between January 1, 2002, and December 31, 2006. After NIP introduction, vaccine coverage rapidly reached >90% [5].

Study Design and Population

We conducted a population-based surveillance study. All in-hospital iGAS-BSI isolates from children aged 0 to 18 years were recorded prospectively starting in January 1990, and invasive GAS all infections (iGAS-all) isolates were cultured from sterile sites (blood, cerebrospinal fluid, pleural effusion fluid, synovial fluid, deep-seated abscesses) starting in January 2005; the surveillance ended in December 2016. Isolates from the throat, ear, eye, superficial skin, and vagina were excluded. Demographic and clinical characteristics were recorded from the electronic medical records. The study was approved by the SUMC's ethics committee.

Microbiology Methods

Microbiological examinations were performed at the SUMC microbiology laboratory using standard protocols. All isolates were sent to the Israeli Ministry of Health Streptococcal Reference Laboratory for *emm* typing. *emm* gene typing was performed following the protocols of the Centers for Disease Control and Prevention [6].

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences 24 (IBM SPSS, Chicago, Illinois). Three periods were defined, (1) the prevaccine period (1990–2002), (2) the transition period (2003–2009) (during introduction of the varicella vaccine to the private market), and (3) the postvaccine period (2010–2016) (after introduction of the varicella vaccine to the NIP).

Comparisons among the 3 periods were performed using the χ^2 or Fisher exact test for comparing rates between unmatched samples, as appropriate. The Student independent-sample t test was used to compare continuous normally distributed variables, and the Mann-Whitney U test was used for continuous variables not distributed normally. A P value of <.05 was considered statistically significant.

RESULTS

Description of iGAS BSI (1990–2016)

Between January 1990 and December 2016, 132 episodes of iGAS BSI occurred. Bacteremic children had a mean age ± standard deviation (SD) of 1.6 ± 3.4 years, 81 (61.3%) were male, 15 (11.4%) had had a recent varicella infection, and 10 (7.6%) had recently had surgery.

Most iGAS BSIs (32.1%) occurred during the winter months (December through February). Children with iGAS BSI had a mean hospitalization length ± SD of 6.0 ± 12.7 days; 15 (11.4%) required intensive care, and 10 (7.6%) needed mechanical ventilation. One child (0.8%) died as a result of GAS sepsis.

The only significant differences between the pre–varicella vaccine and post–varicella vaccine introduction periods were the rates of varicella rash history and infection when the skin was determined to be the port of entry (Table 1).

The most common clinical presentations were bacteremia without a focus (34.4%) and skin and soft tissue infection (SSTI) (29.0%). Fewer SSTIs associated with GAS bacteremia were documented the post–varicella vaccine period than in the prevaccine era (Table 1).

After varicella vaccine introduction, the annual rates of GAS bacteremia per 100 000 children declined from 2.43 (95% confidence interval [CI], 1.73–3.13) to 1.30 (95% CI, 0.91–1.72) between the years 1995–2002 and 2010–2016, respectively (P = .04) (Figure 1). An unexplained peak in iGAS BSI was observed in 2004; similar peaks have also been described in other parts of the world [7, 8].

Description of iGAS-All (2005–2016)

Between 2005 and 2016, 264 episodes of iGAS-all were isolated from soft tissue abscesses (57.0%), joint and bone (20.2%), blood (17.3%), mastoid (3.0%), lung (1.8%), and central nervous system (CNS) (0.7%). The only difference in iGAS-all between the transition and post–varicella vaccine periods was the rates of varicella rash history (Supplementary Table 1).

Children with iGAS-all infection had a mean age ± SD of 4.15 ± 4.9 years, 172 (65.1%) were male, 83 (31.4%) had a coinfection (the most common copathogen was *Staphylococcus aureus*), the mean hospitalization length ± SD was 6.6 ± 9.3 days, and 15 (5.7%) required intensive care. No deaths related to iGAS-all occurred between 2005 and 2016.

Table 1. iGAS-BSI Demographic and Clinical Characteristics Before and After Varicella Vaccine Introduction in Southern Israel, 1990–2002 Versus 2010–2016

Demographic or Clinical Characteristic	Before Varicella Vaccine, 1990–2002 (n = 61)	After Varicella Vaccine, 2010–2016 (n = 29)	*P*
Age (mean ± SD) (years)	1.7 ± 3.6	1.5 ± 2.2	.49
Male sex (n [%])	36 (59.0)	14 (48.2)	.18
Underlying condition (n [%])	10 (16.4)	11 (37.9)	.07
Immunodeficiency (n [%])	3 (4.9)	1 (3.4)	.80
After varicella (n [%])	9 (14.8)	0 (0.0)	.04[a]
After surgery (n [%])	4 (6.6)	2 (6.9)	.60
Port of entry, skin (n [%])	22 (36.0)	6 (20.6)	.03[a]
Hospitalization length (mean ± SD) (days)	5.0 ± 8.4	6.0 ± 10.9	.90
Clinical presentation (n [%])			
SSTI	21 (34.4)	4 (13.7)	.07
Bone and joint infection	11 (18.0)	8 (27.6)	.49
Toxic shock	7 (11.5)	2 (6.9)	.90
Pneumonia	2 (3.3)	2 (6.9)	.63
Mastoiditis	2 (3.3)	1 (3.4)	.81
WBC count (mean ± SD) (10^3/mL)	15.5 ± 7.0	14.2 ± 6.9	.49
Surgical intervention (n [%])	17 (27.9)	8 (27.6)	.95
Need for supplemental oxygen (n [%])	11 (18.0)	4 (13.8)	.70
ICU	9 (13.1)	3 (10.3)	.80
Death (n [%])	1 (1.6)	0 (0.0)	.50

Abbreviations: GAS, group A *Streptococcus*; iGAS BSI, invasive GAS bloodstream infection; ICU, intensive care unit; SD, standard deviation; SSTI, skin and soft tissue infection; WBC, white blood cell.
[a]Statistically significant result.

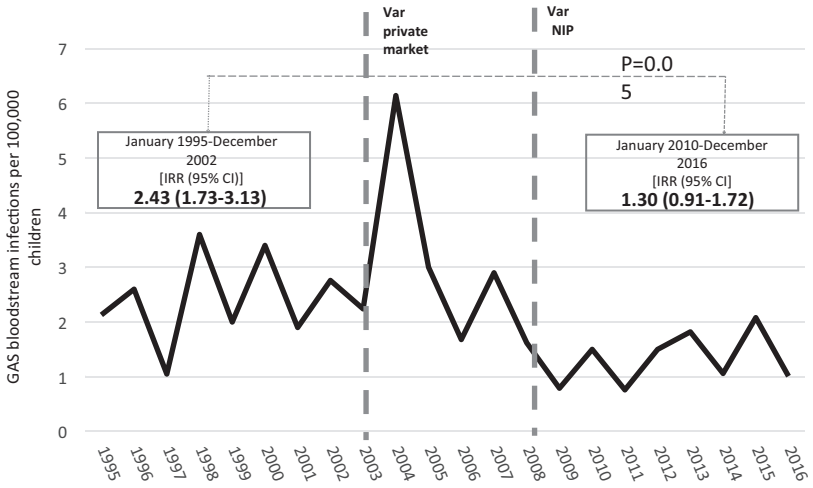

Figure 1. Incidence of group A *Streptococcus* bloodstream infection in children aged 0 to 18 years in southern Israel, January 1995 through December 2016. Shown are incidence rate ratios (IRRs) before and after varicella vaccine introduction. Abbreviations: CI, 95% confidence interval; GAS, group A *Streptococcus*; NIP, national immunization program; var, varicella vaccine.

Microbiologic Description

The rates of antibiotic resistance of the GAS isolates overall to erythromycin and clindamycin were 3.0% and 4.1%, respectively. Higher resistance rates were found in the prevaccine period than in the postvaccine period (7.0% vs 2.5% for erythromycin and 8.8% vs 1.3% for clindamycin, respectively).

A total of 150 isolates were available for genotyping, 42 (44.2%) from the transition period and 108 (67.9%) from the post–varicella vaccine introduction period. The 5 most common iGAS *emm* types were 1.0, 53.3, 33.0, 12.0, and 22.0, which accounted for 43.3% of the isolates. The 10 most common *emm* types are listed in Supplementary Figure 1.

The association between the 5 most common iGAS *emm* types and disease manifestations is shown in Supplementary Table 2. *emm* type 1.0, the most common type (12%), was found in children with BSI or SSTI and in those with a prolonged hospital duration and overall high rates of PICU admissions in children infected with *emm* type 1, compared to rates of PICU admissions in children infected with other *emm* types.

DISCUSSION

Results of this ongoing 27-year surveillance of iGAS BSI in children in southern Israel revealed a reduction in iGAS BSI rates after varicella vaccine introduction along with the disappearance of varicella rash as a predisposing factor.

A previous study that evaluated iGAS BSI in children before varicella vaccine implementation (1993–2002) in a single institution in Israel found that hospitalization rates remained unchanged over time [9].

GAS *emm* type variability influences disease epidemiology [10]. We found an increase in the proportion of our most common *emm* type (1.0) between the pre–vaccine introduction and post–vaccine introduction periods, and this increase was seen most often among children with BSI. However, the number of iGAS-BSI cases decreased between these 2 periods, at least partly because of widespread varicella vaccination.

The association between a universal varicella vaccine and a decrease in the number of varicella-associated iGAS infections was described previously; in those studies, a significant decline in varicella-associated iGAS infections (calculated per 1000 hospital admissions) was found [4, 11].

The strength of this study is that it was population based, and data were drawn from prospective long-term surveillance, which made possible the observation of dynamics over time with a baseline period starting before widespread implementation of the varicella vaccine.

The study has a few possible limitations. First, GAS typing was gradually transitioned from T typing using antisera to *emm* gene typing between 2005 and 2013. Because no comparison could be made between these 2 methods, only isolates with molecular typing were included in the *emm* variability analysis. As a result, data on *emm* baseline before vaccination was not available, and a comparison could be done only between the transition and the post–vaccine introduction periods. In addition, detection of other virulence genes was not part of the study. Second, in contrast to iGAS BSI, which included all blood cultures that were taken from febrile children, iGAS-all was based on isolates cultured from sterile sites, which depended on whether an infection was drained. Because no change in clinical guideline recommendations occurred, we assume that the proportions of deep tissue cultures obtained remained similar over the years. Third, vaccine uptake was based on national data, which might not accurately reflect that in our region. However, we know that the coverage of other routine vaccines

in our region is blank, and therefore we know that the coverage of other routine vaccines in our region is high.

Our findings imply an indirect effect of varicella vaccine on iGAS epidemiology. A GAS vaccine, several of which are in development, is expected to have a greater direct effect. The theoretical coverage of a 26-valent M-protein vaccine for overall iGAS in southern Israel is 68%. A similar theoretical vaccine coverage in the Middle East was found by Steer et al [12]. However, the potential effect of cross-opsonic antibodies is expected to increase coverage rates.

In conclusion, we clearly show that there was a decrease in pediatric iGAS BSI after the introduction of varicella vaccine into the NIP in a population with >90% vaccine uptake. This reduction correlated with the disappearance of varicella rash as a predisposing factor and a reduction in skin and soft tissue manifestations accompanying GAS BSI.

Supplementary Data

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

Note

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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