REGIONAL DIFFERENCES IN THE EPIDEMIOLOGY OF INVASIVE PNEUMOCOCCAL DISEASE IN TODDLERS IN GERMANY

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Abstract: In a population-based study, regional differences in incidence, serotype distribution and resistance rates in invasive pneumococcal disease in 1-2-year-old children were related to different day care attendance rates. Day-care attendance appears to be a relevant risk factor in some German states and should be considered for inclusion in the recommendations for pneumococcal vaccination of children at risk.

Key Words: invasive pneumococcal disease, children's day care, incidence, pneumococcal serotypes, antibiotic resistance

Accepted for publication June 9, 2005.

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The hospital surveillance system was supported by grants from the Foundation for Preventive Pediatrics and additional grants from Wyeth Pharma GmbH (Münster, Germany), Aventis Pasteur MSD (Leimen, Germany) and Glaxo SmithKline (Rixensart, Belgium). The National Reference Center for Streptococci is partly funded by the German Ministry of health and social security and receives support among others by Wyeth Pharma GmbH (Münster, Germany). The laboratory surveillance system running at the Robert Koch Institute receives no external funding.

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DOI: 10.1097/01.inf.0000189985.96561.81

In Germany, the use of the 7-valent pneumococcal conjugate vaccine is recommended for children in defined risk groups. Although the influence of day care on pneumococcal carriage and disease has been described in the international literature,[1–3] this risk factor is not included in the recommendations.

There are regional differences in day care attendance between East and West Federal States in Germany, which are greatest in toddlers. Only 4% of all children at 1–2 years of age in West German Federal States (WG) attend day-care facilities as compared with 55% in East German Federal States (EG).[4] Does this affect the regional epidemiology of IPD in toddlers?

METHODS AND RESULTS

Data obtained in a nationwide prospective study from 1997–2002 on invasive pneumococcal disease (IPD) in children in Germany were analyzed by region (WG and EG) regarding age-specific incidence, distribution of serotypes and antibiotic resistance. Active surveillance of IPD cases was performed in hospitals and, independently, in microbiologic laboratories. Cases were included if they were younger than 16 years of age, if they were hospitalized and if *Streptococcus pneumoniae* was isolated from a normally sterile body site.[5]

RESULTS

Although the overall incidence of IPD in children 0–15 years of age was higher in WG than in EG [4.1; 95% confidence interval (CI), 4.0–4.3) versus 3.0 (95% CI 2.7–3.3) per 100,000 of population], the reverse was true for children age 12–35 months of age [WG 11.0 (95% CI 10.3–11.7) and EG 15.8 (95% CI 13.7–18.0) per 100,000, respectively]. In all other age groups, incidence rates in WG were higher than in EG (Table 1). The same observation was made for pneumococcal meningitis; in all age groups except 12–35 months, the incidence was higher in WG than in EG, whereas the reverse was observed for 12- to 35-month-old children.

The proportion of cases based on blood cultures did not differ significantly by region within the age groups but seemed to be generally lower in older children.

Serotype distribution was different in West and East Germany. Pneumococcal serotypes contained in the 7-valent vaccine were less frequently found in isolates from WG than from EG in the total population under surveillance [0–15 years, 58% (95% CI 55–61%) versus 74% (95% CI 66–80%)]. This difference was significant for age 1–2 years, but because of small numbers of cases, significance could not be proved for the other age groups.

Resistance rates to macrolides (erythromycin A) were higher in children from EG with 37% (95% CI 29–46%) than in WG children with 20% (95% CI 17–23%). The greatest difference was observed in the age group 1–2 years.

DISCUSSION

We found an unexpected peak in the incidence of IPD in EG toddlers 1–2 years of age. In children of this age group in EG, the proportion of cases caused by serotypes included in the 7-valent vaccine was highest, mainly because of the higher percentage of serotype 14. Additionally the proportion of resistant strains was highest in this age group and region.

This finding is unlikely to be caused by chance or bias. The number of reported IPD cases remained stable over time in both regions, accounting for a very constant incidence during the study period of 6 years. Ascertainment bias caused by different blood culturing practices is unlikely. The described regional differences were found for both meningitis and nonmeningitis cases.

Response rates in the reporting systems (data not shown) were constant over time and did not differ between WG and EG in the observational period, indicating no reporting bias by region. Because serotyping was done in a single reference laboratory, all strains were stored and typed under standardized conditions.

Differences in incidence, serotype distribution and antibiotic resistance between IPD cases from EG and WG could not be explained by differences in the prevalence of underlying diseases or reported risk factors (data not shown).

The regional differences in attendance of day care facilities are a tempting explanation for the observed differences in incidence, coverage of vaccine serotypes and antibiotic resistance in the age group 1–2 years between EG and WG. This is the age group with the highest difference in day-care attendance between the 2 regions. Day-care attendance is known to have a major impact on pneumococcal carriage[6–8] as well as on the occurrence of IPD in children and their contacts.[1–3]

Some of the vaccine serotypes are more often related to antibiotic resistance than other serotypes.[6] This is particularly valid concerning macrolide resistance of serotype 14. In our data, serotype 14 alone accounted for 65% of the observed erythromycin A resistance. The higher percentage of serotype 14 in cases from EG is likely to account for the higher resistance rates to macrolides (erythromycin) in children from EG than in WG children.

Attendance of day care is likely to explain the spread of resistant strains and the higher rate of IPD in children 1–2 years of age in EG. There are data showing that acute otitis media and respiratory tract infections are more common in children in day care[9] and that antibiotic treatment is frequently prescribed to shorten the time off day-care during febrile illness.[10] Previous use of

TABLE 1. Surveillance of IPD in Children in Germany, 1997–2002

	<1 yr		1–2 yr		3–4 yr		5–15 yr	
	WG	EG	WG	EG	WG	EG	WG	EG
No. of cases								
Reported	808	90	758	162	319	25	456	48
% with blood culture	73 (69–76)*	68 (57–77)	81 (77–83)	71 (63–78)	78 (73–83)	80 (59–92)	65 (61–69)	48 (34–63)
Incidence								
All IPD	24.4 (23.1–25.8)	16.7 (18.8–20.1)	11.0 (10.3–11.7)	15.8 (13.7–18.0)	4.8 (4.4–5.3)	2.9 (2.0–4.1)	1.2 (1.1–1.3)	0.6 (0.5–0.8)
Meningitis	10.9 (9.9–11.9)	8.8 (6.7–11.5)	3.2 (2.8–3.6)	6.2 (4.9–7.8)	1.5 (1.2–1.7)	1.0 (0.5–1.8)	0.4 (0.3–0.5)	0.3 (0.2–0.5)
Serotyped cases								
N	329	39	334	89	134	14	172	18
% vaccine serotypes	57 (52–63)	62 (45–76)	72 (67–76)	85 (76–92)	65 (56–73)	86 (56–97)	29 (22–36)	33 (14–59)
Resistance								
Tested for erythromycin A	295	37	312	77	121	11	155	15
% resistant	20 (16–25)	27 (14–44)	26 (21–31)	47 (35–58)	19 (13–27)	36 (12–68)	8 (5–14)	13 (2–42)

*Numbers in parentheses, Fleiss 95% CI.

antibiotics is an important factor for the selection of more resistant strains.[8,11]

Although children's day care may be regarded as a possible explanation for the observed regional differences in IPD epidemiology of the 1- and 2-year-olds, there is no good explanation for a lower rate of IPD in other age groups in EG. Underreporting is unlikely, given that capture recapture analyses showed a higher case ascertainment in EG, where 91% of the estimated number of cases was ascertained in comparison with WG with 81%.

The known impact of day care on pneumococcal carriage and occurrence of IPD and spread of resistant strains provide a plausible explanation for the findings in our study, although our data cannot prove that day-care attendance is the cause of the increased risk for IPD in 1- to 2-year-old children in EG. Day-care attendance was not ascertained in cases with IPD precluding the chance to test this hypothesis in a case control study design. Because the causal relation between day-care attendance and an increased risk for IPD has been established in a number of previous studies and documentation of a >10-fold higher day-care attendance rate in toddlers in EG than in WG, the use of day-care facilities is a very likely explanation of the increased rate of IPD in that age group in EG.

ACKNOWLEDGMENTS

We thank the Erhebungseinheit für seltene pädiatrische Erkrankungen in Deutschland for continuous support for this study and all reporting physicians in hospitals and laboratories for their time and efforts. We thank particularly microbial laboratories for providing the isolates.

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