Influence of Day Care Attendance on the Use of Systemic Antibiotics in 0- to 2-Year-Old Children

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ABSTRACT. ***Objective.*** **To examine the association between time spent in different public day care settings and prescription of systemic antibiotics.**

Design. **Population-based cohort study of 5035 Danish children born in 1997 followed from birth to June 30, 1999.**

Methods. **The study was performed by the linkage of records drawn from administrative registries. Exposure was the total time spent in a day care home or day care center. Outcome was the first prescription of a systemic antibiotic. Possible perinatal and sociodemographic confounding factors were considered by statistical analysis.**

Results. **During the first year of life, 39.8% of the girls and 51.1% of the boys received at least 1 antibiotic prescription drug. Enrollment in a day care setting doubled a child's risk of receiving a prescription drug (adjusted relative risk in day care home 1.9, 95% confidence interval: 1.7–2.0; adjusted relative risk in day care center 2.0, 95% confidence interval: 1.7–2.3). Only age confounded the analyses. Age >1 year at the starting time in day care reduced the risk of receiving antibiotic prescriptions during the first 3 months after enrollment.**

Conclusions. **Enrollment in public day care facilities raised the risk of receiving an antibiotic prescription drug to the same extent in day care homes as well as in day care centers, so we cannot recommend one facility over the other based on the present study. Children <1 year old at enrollment were most at risk, suggesting that extension of parental leave may reduce the use of antibiotics.** ***Pediatrics*** **2001;107(5). URL: http://www.pediatrics.org/cgi/content/full/107/5/e76;** ***day care settings, antibiotic use, infectious diseases, children, prescription drug*****.**

ABBREVIATIONS. RR, relative risk; DCC, day care center; DCH, day care home; SA, systemic antibiotics; NDC, not enrolled in day care.

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The increased risk of infectious diseases in day care settings (relative risk [RR] ~2), which has been known about since the postwar period[1–4], is of particular relevance in Denmark where 64% of children aged 6 months to 2 years attend public day care.[5] As use of antibiotics is a morbidity parameter related to infection, it is important from a public health perspective to identify situations and factors associated with high use of antibiotics. Besides discomfort and parental anxiety, infections may give rise to long-term complications, such as mastoiditis and hearing loss after otitis media.[6] Infectious illness also involves economic consequences because of use of health services and parents' absence from work while taking care of sick children.[7] Increased transmission of infectious agents may also result in excess illness among parents, day care staff members, and other children.[8] Furthermore, use of antibiotics is associated with antimicrobial resistance.[9,10]

Information on the association between child care attendance and the use of antibiotics is limited. Most studies were conducted before 1987, and results on risk according to type of day care (ie, day care centers [DCC] or day care homes [DCH]) are contradictory.[1,3,11–14]

This population-based follow-up study analyzes 1) the risk of receiving at least 1 prescription of systemic antibiotics (SA) according to age and gender; 2) the association between total time spent in a day care setting and use of prescription SA; and 3) the risk of receiving at least 1 prescription of SA during the first 3 months after enrollment in day care.

METHODS

Study Population

The study population included all children born during 1997 in the county of Northern Jutland, Denmark, who lived in the county during the entire study period ($n = 5652$). Data were extracted from the North Jutland Birth Registry, which includes information on all pregnancies and births recorded by the midwives. Children who died during the study period were excluded ($n = 40$), of whom 32 died before they reached the age of 4 months. The County of Northern Jutland has 27 municipalities. Because of municipal refusal to participate in the study and lack of usable registrations, we did not have access to information on day care from 5 municipalities, leaving 5035 children for the final analyses.

Day Care Attendance

In Denmark, public day care is administered by the municipalities and organized as DCH, with a single care provider who takes care of 1 to 4 children in the private home, or DCC where 20 to 80 children are cared for in a facility established for that purpose.

Information on day care settings for the 5035 children was obtained for January 1, 1997, through June 30, 1999. We recorded the date of enrollment, date of exit, and type of day care setting. Because of the low number of children attending DCC, we did not distinguish between small or large DCCs. For each child, we calculated the exact period of time enrolled or not enrolled in day care (NDC).

Antibiotic Prescriptions

The outcome measure was defined as the first antibiotic prescription for each child. The National Health Service was used to identify the dates of all SA prescriptions (Anatomic Therapeutic Chemical Code J01) during the period January 1, 1997, to June 30, 1999. In Denmark, antibiotics are purchased by prescription only. All prescription drugs are sold through monopolized pharmacies equipped with computerized accounting systems linked to the Danish National Health Service, which provides tax-supported health care for all citizens and reimburses 50% to 75% of the cost of most prescribed drugs.

We did not have information on drugs not subsidized by the National Health Service, such as cephalosporins and tetracyclines. The relevance of these drugs is negligent; cephalosporins accounted for only 0.2% of the total defined daily doses of antibiotics sold in Denmark during 1996,[15] and tetracyclines are not recommended for children <8 to 12 years old.[16]

Confounding Factors

Information on potential confounders of the association between day care and SA prescriptions was considered. Data from the North Jutland Birth Registry included gender, birth weight (<2500, 2500–4500, and >4500 g), gestational age (<37, 37–41, and >41 weeks), mothers' smoking habits in early pregnancy (yes/no), and marital status (ie, the mother living alone or cohabiting with the father in early pregnancy [yes/no]). We extracted data from the National Statistical Office of Denmark[17] (registered November 1996) concerning older siblings in the home (0/≥1) and the mother's highest educational level: basic school ≤10 years, high school degree, vocational education and training (1–3 years), short-cycle and medium-cycle higher education (1–4 years), or long-cycle higher education (>4 years).

Record Linkage

The study database was established by record linkage of information on day care, perinatal and sociodemographic factors, and prescription data. The linkage was accomplished using the unique personal identification number given to each Danish citizen at birth.

Statistical Methods

To summarize the prescriptions over time, we constructed Kaplan-Meier survival curves, according to age for boys and girls, and compared the curves with the log-rank test.[18]

The follow-up began at the date of birth, and each child contributed to the risk time in the categories DCH, DCC, and NDC with the time they were registered in each category throughout the study period. The censoring date was either date of first SA prescription or June 30, 1999. We calculated the incidence rates, ie, the number of events (children with at least 1 SA prescription) per 100 child-years spent in DCH, DCC, and NDC using Cox regression for the overall population. We estimated the RR (ie, the incidence rate ratio), for the association between day care settings and antibiotic prescriptions. The incidence rate ratio is the incidence rate in DCH or DCC compared with the incidence rate in NDC.[18] The stratification on age was performed by the following age bands: 0 to 5, 6 to 11, 12 to 17, 18 to 23, and 24 to 35 months, based on the Mantel-Haenszel method.

We performed stratified analyses of the potential confounder variables to examine variation across strata (ie, effect modification). The potential confounding of the following variables was examined in Cox regression models: gender, birth weight, gestational age, mother's smoking habits, marital status, siblings, and mother's educational level. In the final models, we included only variables that changed the RR by >10%.[19]

RESULTS

Characteristics of Cohort and Day Care Attendance

Table 1 shows the characteristics of the children in the cohort. By the time of their first birthday, 55.3% of the children had attended public day care (Fig 1). During the study period, 20.9% of the children did not attend day care, 72.3% attended DCH, 4.9% attended DCC, and 1.9% attended both DCH and DCC (mixed).

Use of Antibiotics

Figure 2 shows the cumulative incidence proportions, (ie, the risk of receiving at least 1 SA according to age and gender). The risk was increased for boys ($P < .001$). During the first year of life, 39.8% of the girls and 51.1% of the boys received antibiotics.

Association of Day Care with Prescription of Antibiotics

Table 2 shows the incidence rates of prescriptions in relation to day care. Ninety-nine children received prescriptions per 100 observed child-years of enrollment in DCH for children in age group 0 to 5 months. Enrollment in a day care setting, DCH as well as DCC, doubled a child's risk of receiving a prescription SA (Table 2). The final model only included age because the other potential confounding factors did not change the risk estimate (DCH vs NDC: adjusted RR 1.9 [95% confidence interval: 1.7–2.0] and crude RR 2.5 [95% confidence interval: 2.3–2.6]). Stratification showed a decreasing RR with increasing age. The association between day care and prescriptions was stronger for children without older siblings. The RR did not differ between children enrolled in 1 or 2 types of (mixed) day care settings (data not shown).

Analysis Restricted to Children in Day Care

We restricted the analysis to children attending day care ($n = 3981$) for the analyses of the risk of receiving a prescription after enrollment in the first day care. One third of the children received at least 1 SA prescription during the first 3 months after enrollment. Female gender, age >1 year at start in day care, and no prescriptions before enrollment decreased the risk of prescription (Table 3).

DISCUSSION

Enrollment in a day care setting doubled a 0- to 2-year-old child's risk of receiving a prescription SA, and there was no difference in this respect between DCH and DCC. Children who were enrolled in day care after their first birthday had a lower risk of receiving antibiotics.

The major strengths of our study are its large size, the population-based design, and the prospective data collection on an administrative basis. Hence, we obtained very precise risk estimates. The exclusion of 5 of 27 municipalities was independent of the outcome measure (prescriptions), and this nondifferential selection has presumably not affected the results. All children in the study were followed from birth, and selection bias because of loss to follow-up did not occur. Furthermore, our information on prescrip-

TABLE 1. Characteristics of Children in the Cohort (N = 5035) and Percentages Within Type of Day Care Setting

	Overall %	DCH n = 3639	DCC n = 248	Mixed n = 94	NDC n = 1054
Gender					
Girl	49	48.9	49.2	40.4	49.9
Boy	51	51.1	50.8	59.6	50.1
Birth weight (g)					
<2500	4.7	4.4	5.2	5.3	5.8
2500–4500	91.3	91.5	91.2	90.4	90.5
>4500	4.0	4.0	3.6	4.3	3.7
Gestational age (wk)					
<36	6.0	5.2	7.7	8.5	8.0
37–41	85.2	85.5	82.4	88.3	83.7
>41	8.8	9.2	8.5	3.2	8.3
Mother smoking during pregnancy					
No	72.2	71.5	75.4	69.1	74.3
Yes	27.8	28.5	24.6	30.9	25.7
Marital status					
Single	4.6	4.4	12.1	14.9	2.7
Cohabiting	95.4	95.6	87.9	85.1	97.3
Siblings					
0	40.7	43.4	39.1	46.8	31.0
≥1	59.3	56.6	60.9	53.2	69.0
Mother's education					
Basic school only	28.8	26.6	33.1	34.0	34.9
High school only	3.2	3.4	0.4	2.1	3.5
Vocational education	42.9	45.0	25.4	28.7	41.0
Higher education 1–4 y	20.3	20.7	30.7	10.6	12.0
Higher education >4 y	4.1	3.8	9.7	13.8	2.8
Unknown	0.7	0.5	0.8	–	1.4
Age at enrollment in first day care (mo)					
0–4	3.4	2.6	10.9	12.8	–
5–7	40.1	40.2	37.1	46.8	–
8–12	32.5	32.7	32.3	23.4	–
13–17	16.0	16.2	14.5	14.9	–
18–23	7.1	7.4	3.6	2.1	–
24–35	0.9	0.9	1.6	–	–

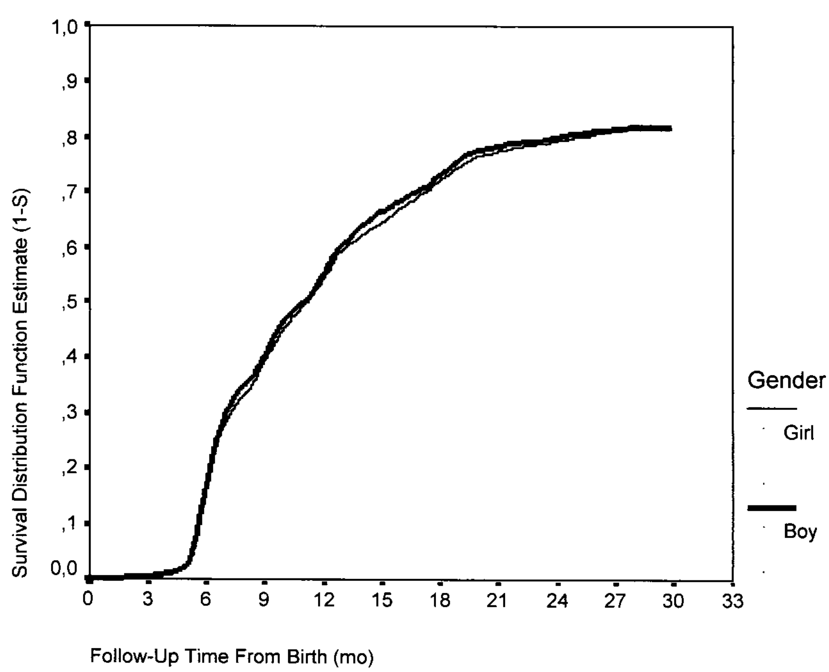

Fig 1. Kaplan-Meier survival curve (1-S). Cumulative incidence proportion of children attending day care setting according to age.

tions could not be biased by knowledge about type of day care, and we were able to control for some confounding factors. Among the weaknesses are the following: 1) Children not enrolled in public day care may have attended private day care arrangements. However, during the study period, all municipalities in the County of Northern Jutland offered a guarantee for a place in public day care after the end of the maternal leave period; 2) Exposure to day care was analyzed by the time notified and not the time the

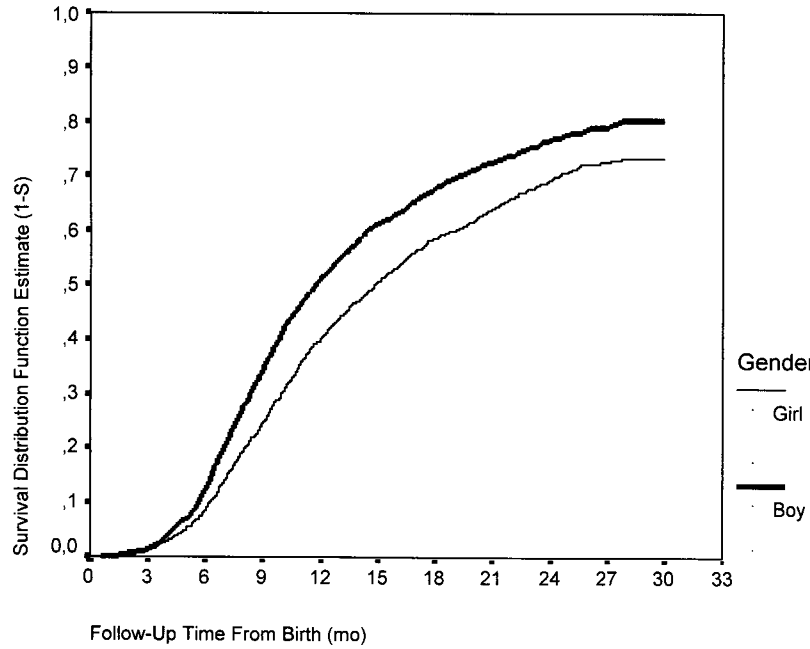

Fig 2. Kaplan-Meier survival curve (1-S). Cumulative incidence proportion of children receiving at least 1 prescription according to age and gender.

TABLE 2. Association Between Time Spent in Day Care Setting and Receiving at Least One Prescription of SA*

	NDC	DCH		DCC	
	Incidence Rate	Incidence Rate	RR (95% Confidence Interval)	Incidence Rate	RR (95% Confidence Interval)
Overall‡	40 (reference)	103	1.9 (1.7–2.0)	111	2.0 (1.7–2.3)
Age group (mo)§					
0–5	20 (reference)	99	4.9 (3.6–6.8)	31	1.5 (0.5–4.7)
6–11	74 (reference)	146	1.9 (1.8–2.2)	170	2.3 (1.8–2.9)
12–17	56 (reference)	96	1.7 (1.5–2.0)	109	2.0 (1.5–2.8)
18–23	51 (reference)	67	1.3 (1.1–1.7)	59	1.2 (0.7–1.9)
24–35	43 (reference)	43	1.0 (0.6–1.7)	75	1.7 (0.6–4.7)
Siblings‡					
0	30 (reference)	110	2.6 (2.3–3.9)	130	3.0 (2.3–4.0)
≥1	48 (reference)	97	1.6 (1.4–1.7)	100	1.6 (1.3–2.1)

* Incidence rate is the number of events (children with at least 1 prescription) per 100 child-years spent in each setting. The RR is the incidence rate ratio shown with 95% confidence intervals, with the reference being incidence rate from NDC.
‡ Cox regression, adjusted for age groups. Adjusting for gender, birth weight, gestational age, smoking, siblings, marital status, and education did not change the risk estimates.
§ Mantel Haenszel method; stratified analysis.

children actually spent in the setting, which may vary among receivers and nonreceivers of prescriptions; 3) Records of antibiotic prescriptions may not have been complete, as children may have redeemed prescriptions while they were away from the county (<2%), and inpatient use was not recorded. The association may be weakened if day care children are hospitalized more often, although most children are discharged from a hospital with a prescription before the end of the treatment period; and 4) Information on smoking during pregnancy, marital status, and education was obtained early in pregnancy. Thus, women may have changed status during the study period. Although few women change their smoking habits, the proportion of smoking women increases postpartum.[20] It is unlikely that the bias would have major implications on our results because change of status was probably independent from the form of day care.

Our findings regarding the cumulative incidence proportions of antibiotic users are similar to those of a Swedish study from Växjö[21] and higher than those reported by Tierp[22] and Jämtland.[23] Comparison with these studies of children born in the 1980s must be cautious, as later Swedish studies have documented a 40% increase in antibiotic prescription rates for children during 1987 to 1993.[24] An American study from 1996, based on questionnaires to parents, showed that 70% of 6-month-old children had used at least 1 antibiotic.[25]

The use of SA was lowest among children cared for at home, as reported in all other studies. Children attending DCC or DCH were facing the same risk of receiving antibiotic prescription drugs, as reported in several Swedish studies.[1,3,11,12] However, Reves and Jones[13] reported that 36% of children in DCC in the United States received antibiotics compared with 7% of children in DCH and 8% of NDC children. Ståhlberg[14] also found that children in DCC had a higher (nonsignificant) risk than DCH children in 1978. This

TABLE 3. Relative Risk of Receiving a Prescription of Systemic Antibiotics During the First Three Months After Enrollment in the First Day Care Setting ($N = 3981$)

	n	Percentage With Prescription	RR (95% Confidence Interval)*
Gender			
Girl	1941	27.3	1.0 (reference)
Boy	2040	37.6	1.5 (1.3–1.6)
Age at enrollment (mo)			
0–4	135	23.7	0.6 (0.4–0.9)
5–7	1598	34.4	1.0 (reference)
8–12	1293	35.0	0.9 (0.8–1.0)
13–17	638	27.6	0.6 (0.5–0.7)
18–23	281	28.5	0.6 (0.5–0.8)
24–35	36	13.9	0.3 (0.1–0.6)
Prescription before enrollment			
No	2954	29.4	1.0 (reference)
Yes	1027	41.6	1.8 (1.6–2.1)
Total	3981	32.6	

* Cox regression, RR estimates incidence rate ratio. Adjusting for confounders was performed in a multivariate model including all the variables present in the table. None of the other potential confounders changed the risk estimate.

variation may spring from cultural differences in the settings or, more likely, from differences in study design. Our study included a large group of children with a follow-up period of >1 year, whereas Reves' and Ståhlberg's studies included fewer children during 8 weeks. Moreover, they may be confounded by skewness in social status, race, and age.

In our study, the RR of receiving prescription antibiotics was lower for day care children who had older siblings compared with children without siblings. This may be attributable to the earlier exposure to infectious agents from the siblings and thereby activation of the immune system, which make them less vulnerable to infections while they attend day care. Another explanation could be improvement of the parents ability to cope with a sick child with the next child.

The Swedish studies showed a slightly lower RR of ~1.5.[1,12] This may be explained by the longer parental leave period in Sweden, which means that most children will not be attending day care until after their first birthday. The difference may stem from different analytic methods. Our study censored the information by the first prescription or at the end of the study period, whereas these other studies counted the total number of prescriptions and divided this number with the total number of child-months in each day care type during the study period.

We did not have information on prescriber behavior or parental attitude. Therefore, the effect ascribed to day care may originate to some extent in parental demand for medication, and not in the degree of infectious illness. Parents who work outside the home may be more disposed to ask for antibiotics for their children to shorten the amount of time that they have to stay away from work.

Our study demonstrated variation in RR in different age groups, and it is one of the first studies to include age on enrollment as a risk factor for use of antibiotics. In Denmark, the parental leave-period extends to ~6 months after delivery. At 6 to 9 months old, humoral immunity is at a nadir.[26] This may partly explain the larger vulnerability to day care exposure among the youngest children, and why age on enrollment in day care affects the risk of receiving prescription SA during the 3 months after enrollment.

Our results indicate that attending DCC or DCH increases the use of antibiotics to about the same degree. In the public planning of future day care services, DCH cannot be given priority over DCC or vice versa based on the present study. Preference to either setting may be rooted in other considerations such as children's emotional and social development. The risk of receiving antibiotics in relation to day care was highest in children <1 year old, suggesting that the extension of parental leave to more than the 6 months offered in Denmark may reduce the use of antibiotics.

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