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## VACCINATION AND THE RISK OF CHILDHOOD ACUTE LEUKAEMIA: THE ESCALE STUDY (SFCE\*)

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## **Abstract**

**Background:** In 2002, a poster alerted the French health authorities to the possibility that the risk of childhood leukaemia might be increased by hepatitis B vaccination. Elucidating the role of vaccination in the etiology of childhood acute leukaemia was therefore included in the objectives of an ongoing national study.

**Methods:** The ESCALE study was a French national population-based case-control study conducted in France in 2003 and 2004 in order to investigate the role of infectious, environmental and genetic factors in 4 childhood neoplastic diseases (leukaemia, lymphoma, neuroblastoma, and brain tumor). The controls were randomly selected from the French population and age and gender frequency matched with the cases. A total of 776 cases of acute leukaemia (91% of the eligible cases) and 1681 controls (69% of the eligible controls) were included. In a specific standardized telephone interview, which was the same for both the cases and controls, each mother was asked to read out her child's complete vaccination record.

**Results:** No association between vaccination and the risk of childhood acute leukaemia (ALL or AML) was observed. No relationship between the risk of leukaemia and the type of vaccine, number of doses of each vaccine, total number of injections, total number of vaccine doses or number of early vaccinations was evidenced. No confounding factor was observed.

**Conclusion:** The study did not show any evidence of a role of vaccination in the etiology of childhood leukaemia.

## Introduction

In 2002, a poster alerted the French health authorities to the possibility that the risk of childhood leukaemia might be increased by hepatitis B vaccination<sup>1</sup>. The potential public health implications of such an association provided the rationale for detailed investigation in the context of the Escale national population-based case-control study of the etiology of childhood cancer. Childhood leukaemia is the most common childhood cancer worldwide. In France, the incidence is 43 cases per million people and per year, equivalent to about 470 new cases diagnosed each year<sup>1</sup>. Very few risk factors, such as high dose ionizing radiation, some chemotherapeutic regimens and some genetic syndromes (Down syndrome, Fanconi syndrome), have been identified. Current research is focusing on infectious, environmental and genetic factors which may influence the risk of childhood leukaemia. Since leukaemia is a neoplastic disease of immune cells, a relationship between immune system events, such as infection, atopic disease or vaccination, and the risk of childhood leukaemia has been suggested. This paper investigates the relationship between vaccination and the risk of the immunologic subtypes of childhood acute leukaemia (AL): acute lymphoblastic leukaemia (ALL) and acute myeloblastic leukaemia (AML).

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<sup>1</sup> Ma X, Does M, Buffler PA, Wiencke JK. Hepatitis B vaccination and the risk of childhood leukaemia. Poster session abstract 3801, American Association for Cancer Research annual meeting, San Francisco, April, 2002

## Methods

The ESCALE study, a national, comprehensive, case-control study conducted in 2003 and 2004, addressed 4 childhood neoplastic diseases (leukaemia, lymphoma, neuroblastoma and brain tumor) and infectious, environmental and genetic potential risk factors.

### *Study population*

Each case of acute leukaemia incident in 2003-2004 in a child aged less than 15 years, residing in France at the time of diagnosis and with no previous history of malignancy was eligible. All the childhood leukaemia cases were confirmed by bone marrow analysis. Children whose mother did not speak French or who had been adopted were not eligible. The cases' mothers were interviewed at least 2 months after diagnosis, within 5 months on average. For ethical reasons, the mothers of children who died before the scheduled interview date were not interviewed. The leukaemia cases were recruited directly by investigators assigned to each French pediatric oncology hospital department, with the support of the French National Registry of Childhood Hematopoietic Malignancies. Out of the 948 cases of childhood acute leukaemia diagnosed in France from January 1, 2003, to December 31, 2004, 860 cases were eligible. The reasons for exclusion consisted in: absence of a biological mother (10 cases); non-French-speaking mother (29 cases); serious psychological disorders (14 cases); physician's refusal (1 case); and death (34 cases). Finally, 776 (91%) case mothers have given their consent and been interviewed.

The controls were randomly selected from the French population using quotas, a priori determined to make the control group representative of all cancer cases in terms of age and gender. Additional quotas constrained the control group to have the same distribution as the national population in terms of number of children living in the household, conditionally to the age group. Random selection was based on a representative sample of 60,000 addresses from the French national telephone directory plus unlisted numbers, which have been randomly retrieved before dialling. Among the 50,217 phone numbers dialled, 27,633 belonged to a household and 8,500 (30.8%) to a target household. Of them, 862 hanged up

before eligibility could have been checked and 5,277 suited to an already completed quota. Finally, among the 2361 eligible control mothers, 679 refused the interview and 1682 (71.2%) gave their consent and were interviewed. We then excluded one control who had a prior history of neuroblastoma, to end with a total number of 1681 controls.

### *Data collection*

Each of the case and control biological mothers responded to a personal and standardized telephone interview lasting 40 minutes. The interview elicited data on demographic and socio-economic characteristics, parental occupational history, childhood environment, familial and personal medical history, and history of the pregnancy.

In France, the vaccination section of a child's medical record contains a separate page for each vaccine. The healthcare professional reports the proprietary name of the vaccine and the date of vaccination on the appropriate page. For the study, each mother was asked to read out each page of the vaccination record, line by line. Each interviewer's computer screen displayed a vaccination record template and an exhaustive list, by record page, of the proprietary names of the vaccines available. Each vaccine administered and the vaccination date were thus obtained. The mother's history of hepatitis B (disease and vaccination) was reported in the same way.

Since combined vaccines are frequently administered, four vaccination parameters were considered: vaccine type; the number of doses of each vaccine (vaccine doses); the total number of injections; and the total number of vaccine doses received (all vaccines taken together). These variables were all treated as categorical variables. For example, 2 DTP (diphtheria + tetanus + poliomyelitis) vaccinations and 1 BCG vaccination are equivalent to 4 vaccines; 2 diphtheria vaccine doses + 2 polio vaccine doses + 2 tetanus vaccine doses + 1 BCG vaccine dose; 3 injections; and a total of 7 vaccine doses. In France, during the 6 first months of life, children usually receive 4 vaccines: BCG, diphtheria, tetanus and poliomyelitis (DTP: usually in one injection). If parents wish, additional recommended vaccines such as

*Haemophilus influenzae* B (Hib) and pertussis vaccines (both combined with the DTP injection) and Hepatitis B vaccine may also be administered. In some contexts, such as chronic disease, the child's physician may also recommend pneumococcal and meningococcal immunization. Pneumococcal immunization has recently been recommended for infants aged less than 2 years attending daycare. During the first 6 months of life, a child may thus receive up to 9 different vaccines, 12 injections and 24 vaccine doses (Figure 1). Vaccination is usually not scheduled for infants aged 6 months to 1 year. Even though the French immunization calendar recommends early vaccination, only four vaccines are mandatory (BCG, diphtheria, tetanus and poliomyelitis) and required for starting school at age 6 years.

#### *Statistical analysis*

The SAS<sup>®</sup> software package (version 8, Cary, North Carolina) was used for all the analyses. Non-conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI), with adjustment for age and gender. In order to compare the different types of leukaemia, analyses were carried out using polytomous logistic regression. Age adjustment for children aged less than 2 years was conducted at intervals of 3 months. For the other age groups, adjustment complied with the stratification categories.

When the exact day of injection was not reported, a default value of 15 was allocated. When the month was not reported, the date was considered missing. Only 25 case mothers (3.2%), consisting in 18 ALL (2.9%), 5 AML (5.5%) and 2 other types of AL, and 34 control mothers (2.1%) did not manage to have their child's immunization records for the interview.

Pre-diagnosis symptoms of childhood leukaemia such as fever, extreme fatigue or bone pain develop, at the latest, 2 or 3 months before diagnosis. As such symptoms may result in the child's physician postponing a scheduled vaccination, the vaccination data were censored at 6 months before the reference date for cases and controls. Similarly, surgery or disease related to a malformation (38 cases and 56 controls) or genetic abnormality (14 cases and 5 controls) may result in a scheduled vaccination date being modified. In consequence, those

cases and controls were excluded from analysis. Thus, out of the 776 cases and 1681 controls who were eligible, 726 cases (3 cases presented with both a malformation and a genetic abnormality) and 1620 controls were included in the analysis. When analyses concerned a given step of the vaccination calendar, only children having reached at least the corresponding age plus 6 months were included, so that both cases and controls could have completed this step. Therefore, analyses made for vaccinations before 6 months and 18 months were carried out among children at least 1 year and 2 years old, respectively.

## Results

Among the 726 cases, 620 (85%) presented with acute lymphoblastic leukaemia, 91 (13%) with myeloblastic leukaemia, 11 (2%) with biphenotypic leukaemia and 4 with acute leukaemia with no immunophenotyping at the date of interview.

The cases and controls did not differ with respect to gender or the number of children living in the household (table 1). There was a small age discrepancy between the cases and controls, particularly for very young children, who were more strongly represented in the control group. The discrepancy simply reflects the fact that the cases were only a fraction of the total case population of the ESCALE study, since only the leukaemia cases are considered herein. There was at least one control for each case in each age group. Cases and controls were similar with respect to age (mean age 6,0 years for controls and 5,6 years for cases), maternal education or degree of urbanization. The paternal educational level was, however, higher for the controls.

About 40% of the mothers reported hepatitis B immunization before pregnancy (301 case and 719 control mothers) while only 25 mothers (6 case and 19 control mothers) reported having had hepatitis B.



At age 6 months, most of the children had been immunized against tuberculosis, diphtheria, tetanus, polio, pertussis and Hib (Table 2). About one third of the children had been immunized against hepatitis B and less than 10% against Meningococcus or Pneumococcus. At age 18 months, most of the children had also been immunized against measles, mumps and rubella (Table 3).

The distribution of hepatitis B immunization was similar for the cases and controls (35.9% vs 35.6%: OR=1,0 [0.8-1.3]), for ALL (34.8% vs 35.6%: OR=1,0 [0.8-1.2]) and for AML (40.8% vs 35.6%: OR=1,3 [0.8-2.1]). The results were unchanged after adjustment for the mothers' hepatitis B status (disease and immunization).

No association between the number of injections received and the risk of childhood leukaemia was observed (table 4). The results were the same for ALL alone and for AML alone. There was no association between the total number of vaccine doses received and the risk of acute leukaemia, ALL or AML.

A child aged 6 months should have received at least 4 injections (1 BCG and 3 DTP). An investigation to determine whether an unvaccinated or less-vaccinated status was associated with a risk of childhood leukaemia was therefore conducted. For all types of acute leukaemia taken together, there was no association between the number of injections or doses received before age 6 months and the risk of childhood leukaemia (table 5). The results were the same for ALL. An unvaccinated or less-vaccinated (1 or 2 injections) status was positively associated with a risk of acute myeloblastic leukaemia. Most of the less-vaccinated children (17/21) had not received BCG vaccine. However, this association observed with injections before 6 months was unstable for AML: the proportion of children with AML unvaccinated or less vaccinated no more differed to that of the controls when we set the threshold for early injections to 4 (31% of children with 3 or more injections in cases and 33% in controls before 4 months) or 8 months (82% of children with 3 or more injections in cases and 86% in

controls before 8 months) instead of 6 months (58% of children with 3 or more injections in cases and 74% in controls before 6 months).

Adjustment for birth order, maternal and paternal educational level and degree of urbanization, which were related to variables such as the number of injections received and age of vaccination, did not modify any of the results for AL, ALL or AML.

## **Discussion**

ESCALE was the first national study to include all the cases of frequent childhood neoplastic diseases (leukaemia, lymphoma, neuroblastoma and brain tumor) diagnosed in France over a two-year period (2003 - 2004). With a 5 % alpha error, the statistical power of the study was greater than 80% for most results.

The study showed no evidence of a relationship between vaccination and the risk of childhood acute leukaemia (ALL or AML), irrespective of the vaccine (including hepatitis B vaccine), total number of injections received or total number of vaccine doses received.

There was no evidence for a relationship between unvaccinated or less-vaccinated status at age 6 months and the risk of acute leukaemia or ALL.

The French National Registry of Childhood Hematopoietic Malignancies includes all the cases of childhood leukaemia diagnosed in the population of mainland France aged less than 15 years since January 1990. The exhaustiveness of the registry has been estimated to be 99.2% for leukaemia<sup>1</sup>. It is therefore probable that almost all the cases diagnosed in 2003 and 2004 were registered. Since there is no evidence for a relationship between vaccination history and the prognosis of leukaemia, the exclusion of early deaths for ethical reasons is unlikely to have induced a selection bias.

The controls were randomly selected from the overall population. The national telephone directory was used as the basis for random selection, given that the subpopulation of telephone owners is comparable to the overall population as regards most sociodemographic characteristics and lifestyle. Unlisted numbers were computer generated prior to the random selection in order to avoid selection bias. The cases and controls did not differ with respect to age (considering all types of cancer) or gender. There was no difference between the controls and overall population with regard to birth order <sup>2-4</sup>, indicating that the quota recruitment process was successful. The controls were representative of the national population in terms of the number of children (0-14) living in the household, which was used as a proxy of birth order, in order to prevent selection bias. Birth order may be, indeed, highly sensitive to the sampling process and may also be related to a number of other variables such as early daycare, early common infections<sup>5</sup> and compliance with the recommended vaccination program<sup>6</sup>. The control mothers' educational level was very similar to that of the French population <sup>2-4</sup> but the control fathers' educational level was higher than that of the overall population. However, the results were unchanged after adjusting for those two variables. A report on childhood vaccinal coverage <sup>7</sup> showed that, in France (1998), 97% of 2-year-old children had been immunized against diphtheria, poliomyelitis and tetanus, 81% against tuberculosis, 82% against measles and rubella, and 96% against mumps compared to 95%, 90%, 88% and 88%, respectively, in the 2-year-old controls in 2003 and 2004.. The immunization status of the controls was thus very similar to that of the overall population.

The vaccination data were as objective as possible since each mother was asked to read out her child's vaccination records line by line. Moreover, in order to prevent recall bias, responses given by mothers unable to consult the vaccination records were considered missing data. Some vaccination records may have been incompletely filled out by the children's physicians. However, this should not have induced differential bias since record completion was independent of case/control status. A recent study has shown that children's personal health record are usually complete <sup>8</sup>. It is therefore likely that vaccination records are also complete. It was difficult to exclude interviewer error in data recording. In order to

minimize the risk of error, particularly that associated with the emotional stress of interviewing cases' mothers, the same standardized questionnaire was used for both the cases and controls and each interviewer interviewed both case and control mothers.

The data on vaccinations 6 months prior to the reference date were censored. However, the results remained unchanged when none of those data were censored.

Most of the cases and controls had been immunized against tuberculosis, diphtheria, tetanus, poliomyelitis, pertussis and Hib at the reference date and very few children had never been vaccinated. There were no differences between the cases and controls. The results with regard to immunization prevalence rates and the lack of association with the risk of childhood leukaemia are consistent with those of most studies<sup>9-13</sup>.

An association between hepatitis B vaccination and the risk of childhood leukaemia has been suggested in a preliminary report from the Northern California Childhood Leukaemia Study<sup>14</sup>. The present study provided no evidence of such an association irrespective of the type of acute leukaemia, age or number of vaccine doses received. These results are consistent with the final results of the Northern California Childhood Leukaemia Study<sup>11</sup> and with the two studies that have investigated hepatitis B vaccination and the risk of acute leukaemia<sup>9</sup>.<sup>11</sup>. This study is the first to include the mother's hepatitis B status in the analysis. Maternal hepatitis B status could not, therefore, have constituted a confounding factor.

Several studies have reported an increasing negative association between the number of vaccine or combined-vaccine injections received and the risk of childhood acute leukaemia<sup>9</sup>.<sup>11-13</sup>. Only one study of the relationship between the overall number of injections and the risk of ALL has been published<sup>13</sup>. It showed the same increasing negative association. None of those studies addressed the relationship between the number of doses received and the risk of acute leukaemia other than ALL. In this study, there was no obvious association between the number of injections received or the number of vaccine doses received and the risk of ALL or AML.

Given that a relationship between a low number of early common infections and the risk of acute leukaemia has been suggested in several articles<sup>5, 15-19</sup>, it was considered pertinent to

address the relationship between delayed early vaccinations and the risk of childhood leukaemia. No relationship between delayed early vaccinations and the risk of ALL was detected. An association was found for AML with fewer injections before the age of 6 months, but it appeared unstable and without any trend as regards the age of injections, suggesting that this association was most probably observed by chance.

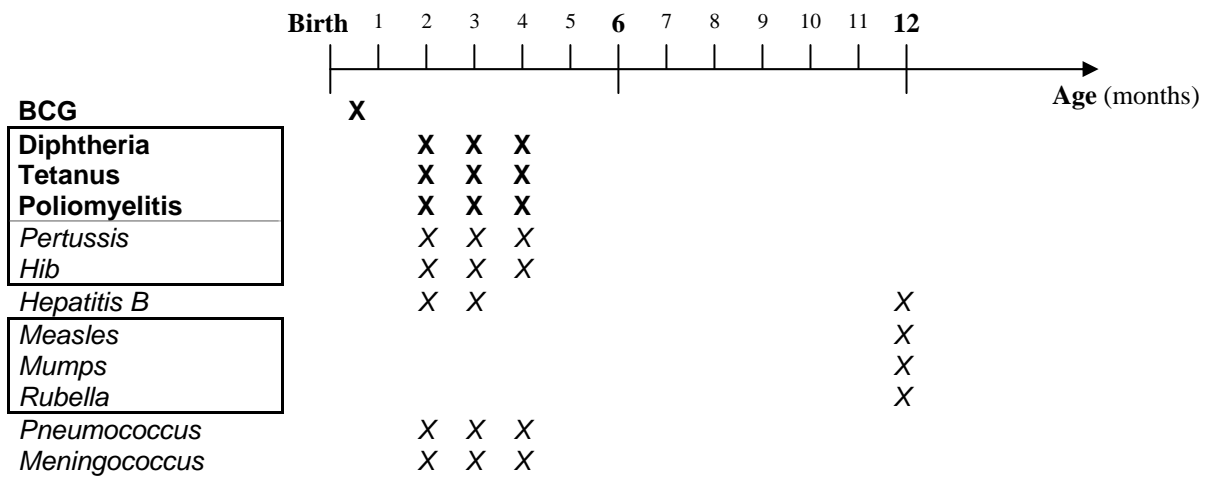
Despite the statistical power of the study (80%), no evidence of a relationship between vaccination and the risk of acute lymphoblastic or myeloblastic leukaemia was evidenced irrespective of the type of vaccine, number of doses or number of early vaccinations.

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**Figure 1: French infantile vaccination calendar (1<sup>st</sup> year of life)**



**Table 1:** Characteristics of the cases and controls

	<b>Cases (n = 726)</b>		<b>Controls (n = 1620)</b>		<b>Control/Case ratio</b>	<b>p</b>
	n	%	n	%		
<b>Gender</b>						ns
Male	395	54.4	892	55.1	2.3	
<b>Age at the reference date (years)</b>						<0.01
< 2	108	14.9	362	22.4	3.4	
2	98	13.5	146	9.0	1.5	
3-4	185	25.5	293	18.1	1.6	
5-6	114	15.7	218	13.5	1.9	
7-8	74	10.2	160	9.9	2.2	
9-11	88	12.1	217	13.4	2.5	
12-14	59	8.1	224	13.8	3.8	
<b>Number of children (0-14 years) living in the household</b>						ns
1	226	31.1	528	32.6	2.3	
2	321	44.2	688	42.5	2.1	
≥ 3	175	24.1	404	24.9	2.3	
Missing data	4	0.6	0	0.0		
<b>Birth order</b>						<0.01
1	362	49.9	685	42.3	1.9	
2	232	32.0	589	36.4	2.5	
≥ 3	132	18.2	346	21.4	2.6	
<b>Daycare</b>						ns
No	634	87.3	1418	87.5	2.2	
Yes	92	12.7	202	12.5	2.2	
<b>Maternal educational level</b>						ns
≤ High school	438	60.3	939	58.0	2.1	
> High school	288	39.7	681	42.0	2.4	
<b>Paternal educational level</b>						0.02
≤ High school	497	68.5	1021	63.0	2.1	
> High school	222	30.6	584	36.1	2.6	
Missing data	7	1.0	15	0.9		
<b>Degree of urbanization</b>						ns
Rural	226	31.1	569	35.1	2.5	
Mixed	171	23.6	367	22.7	2.1	
Urban	315	43.4	658	40.6	2.1	
Missing data	14	1.9	26	1.6		



**Table 2: Vaccines usually administered before age 6 months (children's age > 1 year)**

	<b>Controls (n = 1434)</b> n (%)	<b>AL (n = 696)</b> n (%)	<b>ALL (n = 606)</b> n (%)	<b>AML (n = 76)</b> n (%)
<b>BCG</b>				
Yes	1309 (91.3)	624 (89.7)	548 (90.4)	63 (82.9)
No	94 (6.6)	48 (6.9)	39 (6.4)	8 (10.5)
Missing data	31 (2.2)	24 (3.5)	19 (3.1)	5 (6.6)
<b>Diphtheria</b>				
Yes	1365 (95.2)	663 (95.3)	578 (95.4)	71 (93.4)
No	38 (2.7)	9 (1.3)	9 (1.5)	0 (0.0)
Missing data	31 (2.2)	24 (3.5)	19 (3.1)	5 (6.6)
<b>Tetanus</b>				
Yes	1368 (95.4)	664 (95.4)	579 (95.5)	71 (93.4)
No	35 (2.4)	8 (1.2)	8 (1.3)	0 (0.0)
Missing data	31 (2.2)	24 (3.5)	19 (3.1)	5 (6.6)
<b>Poliomyelitis</b>				
Yes	1366 (95.3)	665 (95.6)	580 (95.7)	71 (93.4)
No	37 (2.6)	7 (1.0)	7 (1.2)	0 (0.0)
Missing data	31 (2.2)	24 (3.5)	19 (3.1)	5 (6.6)
<b>Pertussis</b>				
Yes	1325 (92.4)	646 (92.8)	565 (93.2)	67 (88.2)
No	78 (5.4)	26 (3.7)	22 (3.6)	4 (5.3)
Missing data	31 (2.2)	24 (3.5)	19 (3.1)	5 (6.6)
<b>Hepatitis B</b>				
Yes	510 (35.6)	250 (35.9)	211 (34.8)	31 (40.8)
No	893 (62.3)	422 (60.6)	376 (62.1)	40 (52.6)
Missing data	31 (2.2)	24 (3.5)	19 (3.1)	5 (6.6)
<b>Hib</b>				
Yes	1132 (78.9)	582 (83.6)	512 (84.5)	58 (76.3)
No	271 (18.9)	90 (12.9)	75 (12.4)	13 (17.1)
Unknown	31 (2.2)	24 (3.5)	19 (3.1)	5 (6.6)
<b>Pneumococcus</b>				
Yes	101 (7.0)	30 (4.3)	24 (4.0)	5 (6.6)
No	1302 (90.8)	642 (92.2)	563 (92.9)	66 (86.8)
Missing data	31 (2.2)	24 (3.5)	19 (3.1)	5 (6.6)
<b>Meningococcus</b>				
Yes	71 (5.0)	31 (4.5)	28 (4.6)	2 (2.6)
No	1332 (92.9)	641 (92.1)	559 (92.2)	69 (90.8)
Missing data	31 (2.2)	24 (3.5)	19 (3.1)	5 (6.6)

**Table 3: Vaccines usually administered before age 18 months (children's age > 2 years)**

	<b>Controls</b>		<b>AL</b>		<b>ALL</b>		<b>AML</b>	
	<b>(n = 1258)</b>		<b>(n = 618)</b>		<b>(n = 544)</b>		<b>(n = 62)</b>	
	n	(%)	n	(%)	n	(%)	n	(%)
<b>Measles</b>								
Yes	1110	(88.2)	541	(87.5)	480	(88.2)	50	(80.7)
No	119	(9.5)	55	(8.9)	46	(8.5)	8	(12.9)
Missing data	29	(2.3)	22	(3.6)	18	(3.3)	4	(6.5)
<b>Mumps</b>								
Yes	1103	(87.7)	539	(87.2)	478	(87.9)	50	(80.7)
No	126	(10.0)	57	(9.2)	48	(8.8)	8	(12.9)
Missing data	29	(2.3)	22	(3.6)	18	(3.3)	4	(6.5)
<b>Rubella</b>								
Yes	1104	(87.8)	540	(87.4)	479	(88.1)	50	(80.7)
No	125	(9.9)	56	(9.1)	47	(8.6)	8	(12.9)
Missing data	29	(2.3)	22	(3.6)	18	(3.3)	4	(6.5)

Table 4: Total number of injections and vaccine doses (children's age &gt; 1 year)

	Controls (n = 1434) n (%)	AL (n = 696) n (%)	OR [95%CI] <sup>(*)</sup>	ALL (n = 606) n (%)	OR [95%CI] <sup>(*)</sup>	AML (n = 76) n (%)	OR [95%CI] <sup>(*)</sup>
<b>Total number of injections</b>							
≥10	446 (31.1)	176 (25.3)	ref	148 (24.4)	ref	21 (27.6)	ref
9, 8 or 7	507 (35.4)	229 (32.9)	1.0 [0.8-1.3]	197 (32.5)	1.0 [0.7-1.3]	30 (39.5)	1.3 [0.7-2.3]
6, 5 or 4	380 (26.5)	246 (35.3)	1.3 [1.0-1.7]	223 (36.8)	1.4 [1.0-1.8]	18 (23.7)	0.9 [0.4-1.9]
3, 2 or 1	57 (4.0)	17 (2.4)	0.7 [0.4-1.3]	15 (2.5)	0.8 [0.4-1.5]	2 (2.6)	0.5 [0.1-2.5]
0	13 (0.9)	4 (0.6)	0.7 [0.2-2.2]	4 (0.7)	0.8 [0.3-2.7]	0 (0.0)	
Missing data	31 (2.2)	24 (3.5)		19 (3.1)		5 (6.6)	
<b>Total number of vaccine doses</b>							
≥25	797 (55.6)	352 (50.6)	ref	302 (49.8)	ref	42 (55.3)	ref
24-20	322 (22.5)	197 (28.3)	1.1 [0.9-1.5]	181 (29.9)	1.2 [0.9-1.5]	12 (15.8)	0.7 [0.4-1.5]
19-15	180 (12.6)	85 (12.2)	1.1 [0.8-1.6]	72 (11.9)	1.2 [0.8-1.7]	12 (15.8)	0.9 [0.3-2.2]
14-0	104 (7.3)	38 (5.5)	0.8 [0.5-1.2]	32 (5.3)	0.8 [0.5-1.2]	5 (6.6)	0.7 [0.3-2.1]
Missing data	31 (2.2)	24 (3.5)		19 (3.1)		5 (6.6)	

(\*) Non-conditional logistic regression adjusted on age and gender

Table 5: Total number of injections and vaccine doses before age 6 months (children's age &gt; 1 year)

	Controls (n=1434) n (%)	AL (n=696) n (%)	OR [95%CI] <sup>(*)</sup>	ALL (n=606) n (%)	OR [95%CI] <sup>(*)</sup>	AML (n=76) n (%)	OR [95%CI] <sup>(*)</sup>
<b>Total number of injections before age 6 months</b>							
≥ 4b	684 (47.7)	310 (44.5)	ref	278 (45.9)	ref	26 (34.2)	ref
3	380 (26.5)	207 (29.7)	1.2 [1.0-1.6]	185 (30.5)	1.2 [1.0-1.6]	18 (23.7)	1.3 [0.7-2.4]
2 or 1	266 (18.6)	121 (17.4)	1.1 [0.9-1.5]	97 (16.0)	1.0 [0.8-1.3]	21 (27.6)	2.3 [1.2-4.2]
0	73 (5.1)	34 (4.9)	1.1 [0.7-1.7]	27 (4.5)	1.0 [0.6-1.6]	6 (7.9)	2.2 [0.9-5.7]
Missing data	31 (2.2)	24 (3.5)		19 (3.1)		5 (6.6)	
<b>Total number of vaccine doses before age 6 months</b>							
≥ 10	1052 (73.4)	538 (77.3)	ref	475 (78.4)	ref	51 (67.1)	ref
1 to 9	278 (19.4)	100 (14.4)	0.9 [0.7-1.1]	85 (14.0)	0.8 [0.6-1.1]	14 (18.4)	1.1 [0.6-2.1]
0	73 (5.1)	34 (4.9)	1.0 [0.6-1.5]	27 (4.5)	0.9 [0.6-1.4]	6 (7.9)	1.7 [0.7-4.2]
Missing data	31 (2.2)	24 (3.5)		19 (3.1)		5 (6.6)	

(\*) Non conditional logistic regression adjusted on age and gender

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