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Infant vaccination coverage in 2005 and predictive factors for incomplete or invalid vaccination in Flanders, Belgium: an EPI-survey.

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Abstract

To assess changes in infant vaccination coverage in Flanders since 1999, an EPI-survey was performed in 2005. The parents of 1354 children aged 18-24 months were interviewed at home and the vaccination documents were checked. Several factors possibly related to vaccination status were examined with parametric and non-parametric methods. The coverage rate of recommended vaccines, i.e. poliomyelitis, tetanus-diphtheria-pertussis, H influenzae type b (Hib), hepatitis B, measles-mumps-rubella (MMR) and meningococcal C, reached at least 92.2%, which is a significant rise for MMR, hepatitis B and Hib since 1999. The vaccinating physician, the employment situation of the mother and the family income were significant risk factors for incomplete or invalid vaccination.

Key words: vaccine coverage, risk factors, infants

Abbreviated title: Coverage of recommended vaccines in Flanders' infants, in 2005

1. Introduction

Universal vaccination of infants has been an important tool in controlling infectious diseases in the past century. To attain elimination, high vaccination coverage has to be achieved and maintained [1, 2].

In 1999, an EPI-based survey to measure infant vaccine coverage at 18-24 months-of-age in Flanders (Belgium) demonstrated insufficient coverage for measles-mumps-rubella vaccine (MMR) (82%), hepatitis B vaccine (HBV) (68%) and *H Influenza type b* vaccine (Hib) (86%) [3, 4]. A new, larger survey was performed in 2005. The recommended schedule (table 1) has changed markedly since 1999, and all recommended vaccines are now offered free of charge. In 2001, the mandatory oral polio vaccine was replaced by the inactivated vaccine (IPV) and included in a combination vaccine with tetanus-diphtheria-pertussis (DTP). In addition, the conjugated serogroup C meninogococcal vaccine (MenC) was added to the schedule. In January 2004, a hexavalent DTP-IPV-Hib-HBV vaccine was introduced. However, the birth cohort of which children were recruited for this study largely received the 2003 schedule with three monovalent doses of HBV. A number of characteristics that have been found to be related to vaccination coverage in industrial countries have been taken into consideration in this 2005 survey, such as parental education, ethnicity, age, marital and working situation, birth order of the child, medical problems, side effects of vaccination, vaccine provider and having a vaccination card [3, 5-18].

This article presents the current vaccine coverage in infants aged 18-24 months in Flanders and the risk factors that were identified for incomplete vaccination. Additionally, we assessed the validity of each schedule according to minimum age and interval parameters, and evaluated risk factors for not having received a complete and valid schedule independently.

2. Methods

2.1 Survey design

A sample of 1500 infants born between 30/6/2003 and 15/11/2003 and officially registered as resident in Flanders was selected using an EPI-based two-stage cluster survey [5, 6, 19]. Firstly, we selected a population-proportionate sample of municipalities, stratified over the five Flemish provinces proportionally to the size of their birth cohort in 2003. In a second stage, the National Register randomly selected twelve infants and four replacements per cluster. To calculate the sample size, the margin of error for the 95% confidence interval was

set at 0.025, assuming a design effect of 2. Trained interviewers visited the selected families at home and transcribed the vaccination data from the vaccination card. Permission to contact the physician who had vaccinated the child was requested. Additional information was retrieved from the parents using a standardised questionnaire. The study was approved by the Antwerp University Hospital Ethics Committee and by the National Privacy Commission. Written informed consent was obtained from a parent or caretaker of each included child.

2.2   Definitions

For the analysis of risk factors, two main outcome factors were defined, according to the number of doses in the recommended vaccine schedule and the guidelines on minimum acceptable age per dose and minimum acceptable interval between doses approved by the Belgian National Health Council (w1), which are almost identical to those approved by the Advisory Committee on Immunization Practice of the United States of America [20, 21](see Table 1). Firstly, we defined a complete schedule as four doses for IPV, DTP and Hib, three doses for HBV and one dose for MMR and MenC. Secondly, we defined a valid schedule as a complete schedule strictly respecting all minimum age and interval parameters. For MenC, three doses with an interval of at least four weeks, starting at the age of 8 weeks or later, was also a valid schedule, according to recommendations by the manufacturer. The main vaccinator was defined as the physician who administered the highest number of vaccine doses, not counting DTP and Hib doses because they were usually given in a combined vaccine with IPV.

2.3   Statistical analysis

For all analyses, the survey design was taken into account and weighting was performed when necessary. Doses not documented on the vaccination card at home or in a medical file, were considered as not given.

Characteristics associated with either incomplete or invalid vaccination were analysed for each vaccine as well as for the whole schedule. To deal with the large number of characteristics (23 in total) included in the survey, we supplemented logistic regression with non-parametric classification tree analysis and random forests [22, 23]. Classification tree analysis constructs disjointed subsets of data using the characteristics that explain the outcome variable in the best way. A random forest summarizes a set of possible classification trees, based on bootstrap samples, and orders the variables according to their frequency of

appearance as first parent nodes. Based on classification trees predicting either incomplete or invalid vaccination, variable importance lists were generated and, using a visual cut-off , a limited number of characteristics was selected for use in a stepwise logistic regression analysis. Associations were considered significant if the p-value did not exceed 0.05. Vaccine coverage analysis and logistic regression were performed with Stata 9 and non-parametric analyses with R 2.3.1.

3. Results

3.1 Study population

Between May 10th 2005 and July 31st 2005, 1476 families with a child aged 18-24 months were visited at home, 226 (15.3%) of them were replacements for families that could not be reached. Among the families visited at home, 117 (7.9%) refused to take part, mainly mentioning reasons as "Not interested" or "No time". Those families were not replaced to limit the risk of selection bias. In addition, five questionnaires were lost. Most socio-demographic parameters of the study population were comparable to other data about Flemish children under 3 years-of-age, except for the gender distribution which was 53% girls and 47% boys, compared to 48.8% and 51.2% in the reference population. This was adjusted for by weighting, which necessitated the exclusion of five children who were all fully vaccinated, leaving data from 1349 children for analyses.

3.2 Coverage rate of recommended vaccines

The coverage rate per dose is presented in Table 2. No vaccination could be documented for 12 (1%) children. For 141 (10.5%), one or more doses were missing from the recommended schedule. The majority of children was immunized by a public health organisation called "Child and Family" in well-baby clinics (80.9%) or in day-care centres (2.3%). The others were vaccinated privately by their paediatrician (10.9%) or general practitioner (5.3%), and 0.6% received their vaccines abroad. Vaccination coverage in replacements was not statistically different from the whole group.

3.3 Factors related to incomplete or invalid vaccination

The variable importance lists were very similar for all vaccines and for both outcome factors, Figure 1 presents the result for complete IPV vaccination as an example. The four most important variables in any list were the maternal age, the paternal age, the employment

situation of the mother, and the main vaccinator. The next five variables were the province of residence, the maternal educational level, the paternal educational level, the family income and the age of the child. A visible cut-off could be distinguished after the nine variables described above for most of the models. For the models predicting complete vaccination with DTP, Hib, HBV or MBR, the child's age was not retained. For both MenC models, use of day-care was retained as a tenth factor and for the model predicting valid vaccination, the number of siblings was an eleventh factor.

To avoid co-linearity in the logistic regression analysis, correlation between maternal and paternal factors was sought and was found to be significant for age and educational level. It was therefore decided to retain only the maternal age and educational level as a proxy for both parents.

The final regression models are presented in Tables 3 and 4. The main vaccinator was significant in all models. Compared to children mainly vaccinated by a paediatrician, children mainly vaccinated by a family physician were less likely to be completely vaccinated and also to have received a valid schedule, whereas children vaccinated in a well–baby clinic or day-care centre were more likely to have received a valid schedule. The latter were also more likely to have received the complete total recommended schedule regardless of validity concerns, but in the models for the separate vaccines this was significant only for HBV and MMR.

Other significant characteristics were the employment situation of the mother and the family income. With a full-time working mother, valid vaccination was more likely with IPV, DTP, Hib and HBV and also with the total schedule as a whole, whereas valid MMR vaccination was more likely if the family income was higher then €1500 per month. Looking at the number of doses, a full-time working mother was a significant factor only for complete DTP and Hib vaccination.

To find out if the parents' choice of the main vaccinator could be predicted by the other characteristics from the survey, we decided to perform an additional analysis, applying the same strategy as described above. Random forest indicated the age of each parent, the employment situation of the mother, the province of residence, the family income, the educational level of each parent, the preferred physician when the child was ill, the age of the child and the use of day-care as most important variables. Logistic regression showed that older mothers ($p<0.001$) and mothers living in more populated provinces ($p<0.05$) were

significantly more likely to choose a paediatrician as main vaccinator, whereas parents preferring to consult a paediatrician when the child was ill were significantly less likely (p<0.05) to go there for vaccination (data not shown).

4. Discussion

This survey showed an important increase in infant vaccine coverage at 18-24 months age in Flanders in 2005 compared to the survey performed in 1999, especially for MMR (10.6% rise), HBV (23.8% rise for the third dose), and Hib (18.7% rise for the fourth dose) [3, 4]. For HBV and Hib this can be explained by the increase in reimbursement, from partially refunded to free of charge. The rise of the MMR coverage may be related to advancing the recommended age from 15 to 12 months, together with the higher participation rate to the services of well baby clinics during the first year of life. Moreover, each recommended vaccine had a coverage higher than 90%, which is the current goal of the WHO (w2). Comparison to other European countries is difficult due to differences in the recommended number of doses per vaccine. The coverage of MMR and the fourth dose of DTP reported to the WHO (w3) in 2004 by Denmark, Finland and the Netherlands exceeded 93%, except for the fourth dose of DTP in Denmark (87%). In Italy, an EPI-survey conducted in 2003 found 95.7% for the third dose of HBV, but only 76.9% for MMR [5]. A large-scale survey performed in the UK in 2002-2003, recorded 3.3% of partially immunised and 1.1% of non-immunised infants at 9 months-of-age for the recommended vaccine schedule as a whole [8].
If non-valid schedules were excluded, the coverage per vaccine dropped with 3.6% to 7.6%. Validity assessments are rarely performed, though administering vaccine doses too early can impair the immune response to some vaccines [24]. In the majority of the 45 countries they evaluated, Murray et al found that the officially reported coverage of the third dose of DTP differed more than 20% with the valid coverage rate, that considered only doses given in accordance to the schedule [25]. In the US, excluding invalid doses lowered the coverage per vaccine with 0.7% to 6.5% [24].

The various statistical models used to identify risk factors for being incompletely or invalidly vaccinated produced similar results. In the logistic regression analysis, the physician who administered most of the vaccine doses was the main predictor of both outcome factors, whereas the working situation of the mother and the family income were predictive of invalid vaccination. Random forest analysis indicated that parental age and education, the province of residence and the age of the child could also be important, but they were not significant in the

logistic regression analysis. Results of both methods should be seen as complementary. If they confirm each other, the evidence for the existence of an association is stronger. In statistical analyses, it is a standard approach to use nonparametric techniques to validate and complement parametric methods, since the latter inevitably rely on model assumptions. Moreover, nonparametric techniques can be used as data mining and variable selection tools (see e.g. Moons et al. [26]). However, only logistic regression can demonstrate significance at a 5% level.

Children vaccinated in a well-baby clinic, a public health service offering preventive child care free of charge, were significantly more likely to have received a valid schedule than children vaccinated by a paediatrician or a family physician, both private physicians. Interestingly, a random forest analysis indicated that the parents' choice of the main vaccinator could be influenced by the same determinants as vaccination but unfortunately, regression analysis did not add much useful information. In the 1999 survey in Flanders, the main vaccinator was found to be associated with the educational level of the parents [4]. The vaccine provider was also found to be a significant determinant of vaccination in some US studies [10, 11] and physician factors were found important in surveys questioning the reason for non-vaccination [3, 18, 27].

Our finding that full-time working mothers were significantly associated with complete and valid vaccination is consistent with findings in the UK [8]. Possibly a higher educational level, a higher income or better access to information could explain this. The family income was significant only in the regression models predicting incomplete polio vaccination and invalid MMR vaccination, where the maternal employment situation was not significant. Maternal and paternal educational level and age were found to be important in the non-parametric analysis only. In other studies, including a previous study in Belgium [3, 6, 12, 14], low parental educational level was significantly associated with incomplete vaccination and maternal age has also been recognized as a factor influencing vaccination [6, 8, 12, 13]. Having a single parent, a high number of siblings or having older siblings were not found to be associated to vaccination in this study, although they were in other studies [8, 11, 13, 14, 16, 18, 28]. The degree of urbanisation was not predictive either, which is reassuring because a lower coverage in urban regions could elicit a risk of transmission for some diseases.

A limitation of the study was that the participation rate in the original sample was below 80%, due to replacements and refusals that were both more frequent than in the 1999 survey. Selection bias cannot be ruled out, but the socio-demographic profile of the study population

was comparable to that of the reference population. Replacement did not introduce selection bias as the coverage was the same in replacements as in the original sample population. The vaccine coverage in the study population could be underestimated as only documented doses were considered, but maximum effort was put into obtaining missing data from medical files. Strengths of this study were that the validity of the schedule was taken into account and that the same methodology was used as for the 1999 survey, which allows for comparison of the results of both studies.

We conclude that infant vaccine coverage in Flanders has markedly increased since 1999. It is, however, important to preserve this high coverage. As children who where vaccinated outside well-baby clinics were less likely to be completely vaccinated, future research should focus on the underlying reasons and possible ways to support private physicians consulted for vaccinations.

URL addresses to be added in the text:

w1

http://www.health.fgov.be

w2

http://www.who.int/vaccines-documents/

w3

http://data.euro.who.int/cisid/

Contributors: HT, CV, AD, MR, KH and PVD were all involved in coordination and design of the study of vaccine coverage in Flanders in 2005, that covered different age groups. NH,

MA, and HT analysed and interpreted infant data for this manuscript. HT wrote the first draft of the paper. All other authors critically reviewed the draft. PVD and HT are the guarantors.

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Table 1: Recommended vaccination schedule in 2003 and 2004, and minimal acceptable age per dose, as approved by the Belgian National Health Council

Recommended Age	2003					2004		
	DTPa-IPV	Hib	HBV	MMR	MenC	Hexavalent	MMR	MenC
2 months	6 weeks	6 weeks	-	-	-	6 weeks	-	-
3 months	10 weeks[1]	10 weeks[1]	birth	-	-	10 weeks[1]	-	-
4 months	14 weeks[1]	14 weeks[1]	4 weeks[1]	-	-	14 weeks[1]	-	-
12–13 months	-	-	-	12 months	12 months[5]	-	12 months	12 months[5]
13-18 months	12 months[2]	12 months[3]	6 months[4]	-	-	12 months[2]	-	-

Legend: All recommended vaccines are offered free of charge. A different combination vaccine was available free of charge in 2003 compared to 2004. DTPa= diphtheria-tetanus-acellular pertussis vaccine, IPV= inactivated poliomyelitis vaccine, Hib= H. influenzae type b vaccine, HBV= hepatitis B vaccine, MMR= measles-mumps-rubella vaccine, MenC= conjugated meningococcal C vaccine, hexavalent = IPV-DTPa-Hib-HBV combination vaccine

[1] additionally, a minimal acceptable interval of 4 weeks with the previous dose has to be respected

[2] additionally, a minimal acceptable interval of 6 months with the previous dose has to be respected

[3] additionally, a minimal acceptable interval of 8 weeks with the previous dose has to be respected

[4] additionally, a minimal acceptable interval of 8 weeks with the previous dose and 16 weeks with the first dose has to be respected

[5] for a single dose schedule

Table 2 : Vaccine coverage in infants aged 18-24 months in Flanders in 2005, in percent (with 95% confidence interval) (n=1349)

	Dose 1	Dose 2	Dose 3	Dose 4
IPV	99.0	98.6	98.2	93.1
	(98.5-99.5)	(97.9-99.2)	(97.4-989)	(91.8-94.4)
DTPa	98.7	98.2	97.9	92.9
	(98.1-99.3)	(97.4-99.0)	(97.0-98.8)	(91.6-94.2)
Hib	98.1	97.6	97.2	92.6
	(97.4-98.8)	(96.7-98.5)	(96.3-98.2)	(91.2-94.0)
HBV	96.9	96.1	92.2	10.1
	(95.9-97.9)	(94.9-97.3)	(90.8-93.7)	(8.2-11.9)
MBR	94.0			
	(92.6-95.3)			
Men C	94.1			
	(92.8-95.4)			

Legend: IPV= inactivated poliomyelitis vaccine, DTPa= diphtheria-tetanus-acellular pertussis vaccine, Hib= H. influenzae type b vaccine, HBV= hepatitis B vaccine, MMR= measles-mumps-rubella vaccine, MenC= conjugated meningococcal C vaccine

Table 3: Odds ratio's for having received a complete schedule for each recommended vaccine and for the total recommended schedule, from logistic regression models (n=1349)

	HBV	IPV	DTPa	Hib	MenC	MMR	Total schedule
% completely vaccinated	92.2	93.1	92.9	92.6	94.1	94.0	88.5
Main vaccinating physician[1]							
Well baby clinic or day-care	**2.69*****	1.73	1.68	1.68	1.22	**2.29***[2]	**3.03*****
Family physician	**0.24*****	**0.20*****	**0.18*****	**0.13*****	**0.16*****	**0.27****	**0.32*****
Baseline: paediatrician	1	1	1	1	1	1	
Mother's employment situation							
Not full-time or not salaried			1.21	1.25			
Full-time salaried			**2.34***	**2.44****			
Baseline: Not working			1	1			
Family income							
< € 800 per month		PS					
€ 800 - € 1500 per month		0.63					
€ 1500 - € 2000 per month		0.93					
€ 2000 - € 3000 per month		**2.08***[3]					
> € 3000 per month		1.49					
Baseline: unknown income		1					

Legend: IPV= inactivated poliomyelitis vaccine, DTPa= diphtheria-tetanus-acellular pertussis vaccine, Hib= H. influenzae type b vaccine, HBV= hepatitis B vaccine, MMR= measles-mumps-rubella vaccine, MenC= conjugated meningococcal C vaccine, total schedule= total recommended schedule (table1), PS= perfectly predicting complete vaccination.
Odds ratio's are only presented for factors with at least one significant category. Odds ratio's printed in bold are significant with *p < 0.05; ** p<0.01, *** p<0.001.
[1] the category "not vaccinated" is not presented in the table, as all models perfectly predicted incomplete vaccination in this category
[2] p=0.042
[3] p=0.047

Table 4: Odds ratio's for having received a complete and valid schedule for each recommended vaccine and for the total recommended vaccination schedule, from logistic regression models (n=1349)

	HBV	IPV	DTPa	HIB	MenC	MMR	Total schedule
% complete and valid vaccination	88.6	85.5	85.6	86.4	88.3	90.1	74.7
Main vaccinating physician[1]							
Well baby clinic or day-care	**1.79***	**2.08****	**2.14****	**2.14****	**1.88****	1.67	**2.39*****
Family physician	**0.23*****	**0.30****	**0.35****	**0.29*****	**0.40****	**0.31****	**0.32*****
Baseline: paediatrician	1	1	1	1	1	1	1
Mother's employment situation							
Not full-time or not salaried	1.16	1.09	0.96	0.91			1.09
Full-time salaried	**2.05****	**2.34*****	**1.73***	**1.60**[*2]			**1.75****
Baseline: Not working	1	1	1	1			1
Family income							
< € 800 per month						1.16	
€ 800 - € 1500 per month						1.58	
€ 1500 - € 2000 per month						**2.64***	
€ 2000 - € 3000 per month						**2.23***	
> € 3000 per month						**2.08***	
Baseline: unknown income						1	

Legend: IPV= inactivated poliomyelitis vaccine, DTPa= diphtheria-tetanus-acellular pertussis vaccine, Hib= H. influenzae type b vaccine, HBV= hepatitis B vaccine, MMR= measles-mumps-rubella vaccine, MenC= conjugated meningococcal C vaccine, total schedule= total recommended schedule (table1), PS= perfect success.
Odds ratio's are only presented for factors with at least one significant category. Odds ratio's printed in bold are significant with $*p < 0.05$; ** $p<0.01$, *** $p<0.001$.
[1] the category "not vaccinated" is not presented in the table, as all models perfectly predicted incomplete vaccination in this category
[2] $p=0.041$

Figure 1: Variable importance list for completeness of IPV vaccination