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ORIGINAL ARTICLE

Dutch national immunization schedule: compliance and associated characteristics for the primary series

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Abstract In the Netherlands, the recommended priming immunization schedule for diphtheria, tetanus, pertussis and polio (DTaP-IPV) is at 2, 3 and 4 months of age. We evaluated the compliance with the recommended schedule, as well as its characteristics. We included all infants born between 2007 and 2012 who received minimally one DTaP-IPV vaccination (n = 1,061,578). Infants complied with the schedule if they received the first vaccination between 6 and 9 weeks of age, and the second and third vaccination 2–6 weeks after the first and second vaccination. We examined associations between compliance and several characteristics using log-binomial regression. Compliance for the first, second and third vaccination was 81.6, 88.3 and 84.2%, respectively. Compliance with the total recommended schedule was 64.5%, and increased from 60.1% for 2007 to 68.5% for 2012. Compliance was higher for full-term infants (65.9%), infants with normal birth weight (66.0%) and when both parents were born in the Netherlands (66.8%).

Conclusion: Delayed vaccination during the primary vaccination schedule occurs in one sixth of the Dutch children. Efforts to improve compliance should be focused in particular on preterm infants, infants with low birth weight and infants whose parents are not born in the Netherlands.

What is Known:
- *A delayed start of vaccination leads to a longer period at risk for infectious diseases,* e.g. *pertussis*
- *Delayed vaccination is associated with several factors including prematurity, low birth weight, family size, birth order, low socioeconomic status and health status of the child*

What is New:
- *Compliance with the recommended priming immunization schedule for diphtheria, tetanus, pertussis and polio was 64.5%, and increased from 60.1% for 2007 to 68.5% for 2012*
- *If the first vaccination was delayed, there was a higher chance that the following vaccinations were administered 'out-of-schedule' as well, resulting in even a higher age at second and third vaccination.*

Keywords Vaccination · Vaccination timeliness · Vaccination compliance · Immunization schedule

Abbreviations

BW	Birth weight
CHC	Child health clinics
DTaP-IPV-Hib-HepB	Diphtheria, tetanus, acellular pertussis, inactivated polio, Hib and HepB
DTwcP-IPV	Diphtheria, tetanus, whole-cell pertussis and polio

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GA	Gestational age
HepB	Hepatitis B
Hib	Haemophilus influenzae type b disease
NIP	National Immunization Programme
PCV	Pneumococcal conjugate vaccine
PR	Prevalence ratio
SES	Socioeconomic status
SGA	Small for gestational age

Introduction

Immunization prevents an estimated annual two–three million deaths from diphtheria, tetanus, pertussis and measles worldwide [25]. In the Netherlands, a high vaccination coverage (for infants, uptake is 95% or higher) decreased the incidence of these diseases dramatically, compared with the prevaccine era [9, 11]. Besides the fact that immunization averts deaths, it also prevents disability and serious illness [1].

To protect infants against certain infectious diseases, the Dutch National Immunization Programme (NIP) has been implemented in 1957 and is coordinated and evaluated by the Dutch National Institute for Public Health and the Environment (RIVM). Today, the NIP includes vaccination against diphtheria, tetanus, polio, pertussis, *Haemophilus influenzae* type b disease (Hib), measles, mumps, rubella, meningococcal C disease, pneumococcal disease (10 serotypes), cervical cancer (human papillomavirus type 16/18) and hepatitis B (HepB). In the Netherlands, it is recommended to start with the first diphtheria, tetanus, acellular pertussis, inactivated polio, Hib and HepB (DTaP-IPV-Hib-HepB) combination vaccine at 2 months of age, i.e. between 6 and 9 weeks of age, followed by the second and third vaccination each within a 4-week interval after the previous vaccination. After the primary series, booster vaccinations are recommended at 11 months (DTaP-IPV-Hib-HepB), 4 years (DTaP-IPV) and 9 years (DT-IPV) of age. The current schedule is the result of several adaptations, e.g. adding more vaccines, replacing separate vaccines by a combination vaccine and changing the timing of the vaccinations to improve protection against infectious diseases [5]. For example, in 1999, the accelerated infant schedule of diphtheria, tetanus, whole-cell pertussis and polio vaccination (DTwcP-IPV) was adopted, with a start at 2 months instead of 3 months aiming to protect infants earlier against in particular pertussis.

Sustaining high vaccination coverage is essential to protect the population against these infectious diseases. Insight in adequate timing of vaccination can provide important information. Namely, incomplete and unvaccinated infants are at risk of for example severe pertussis since pertussis is endemic [14]. Furthermore, the compliance to the schedule by background characteristics including not only prematurity, socioeconomic status (SES) and ethnicity but also the executive organization can provide insight into which efforts could improve compliance. Woestenberg et al. [24] examined the timeliness of the first DTaP-IPV vaccination. However, to monitor the Dutch NIP carefully, the evaluation should also include the timeliness of subsequent vaccinations. Therefore, we examined the compliance with the primary series of DTaP-IPV, recommended as a 2–3–4-month schedule, and assessed which determinants influenced compliance with the primary series.

Materials and methods

Data source and study population

We used data from Præventis, a national immunization register in which all administered vaccinations of the NIP are registered. Præventis has a link with the population register and is used to invite parents of infants eligible for the NIP [13]. The database also contains data from the newborn screening that takes place within 7 days after birth, which includes the duration of pregnancy and birth weight of the infant as reported by the parents [18].

The study population included all infants born in the Netherlands between January 1, 2007 and December 31, 2012, who were registered in Præventis at February 7, 2014, had a known residence and received minimally one valid DTaP-IPV vaccination (approximately 97% of all children in each birth cohort do receive at least one DTaP-IPV vaccination).

An immunization is considered invalid when, e.g. the vaccine is administered too early (before 4 weeks of age) or when the interval between two vaccinations is shorter than 2 weeks. Note that a vaccination given between 4 and 6 weeks of age is considered valid. However, this early and off-label administration of the vaccine is only recommended in specific situations including a local pertussis outbreak or a baby with direct contact with a pertussis patient, extensive and contaminated wounds, in particular, second- and third-degree burn wounds and travel to a risk country [4]. We excluded infants who were deceased, left the Netherlands within 1 year after birth or had an unknown or unclear vaccination administration date. In this study, we only investigated the vaccine component DTaP-IPV; in daily practice, the combination vaccine DTaP-IPV-Hib(-HepB) was administered in the study period (2007–2012) simultaneously with the 7-valent and, from 2011, 10-valent pneumococcal conjugate vaccine (PCV7/PCV10), so the results will be largely applicable to those vaccines as well.

We extracted anonymous data from Præventis including background characteristics (date of birth, gender, current residence, country of birth of the parents), DTaP-IPV vaccination (date of administration, executive organization: child health clinics (CHC), general practitioner or hospital) and newborn screening (gestational age (GA) and birth weight (BW)). The lowest level for current residence was the municipality, to ensure the privacy of the infants. Based on municipality, we categorized the infants into one of the 25 public health service regions of the Netherlands in 2014 [15].

SES and urbanization rate were not available at individual level in Præventis. Therefore, we used data per municipality from the Netherlands Institute for Social Research (SES) and Statistics Netherlands (urbanization rate) as a proxy for the individual value [21, 22]. SES is an indicator based on the average income per household in a particular postcode area as well as the percentage of households with low income, with a low education level and without a paying job [8].

The Dutch National Immunization Programme

Parents are invited by letter, including personalized vaccination cards for each vaccination event, to have their infants vaccinated according to the NIP. If parents do not respond to the invitation, a reminder is sent. The vaccinations are administered during routine visits at regional level by a network of child health clinics (CHC) and regional public health services. The attendance to these routine visits is very high, up to 99% [23]. In addition to the vaccinations, these visits also include physical check-ups with full medical history, screening of growth and development and vision and hearing testing. Vaccination is voluntary and free of charge [4].

Compliance with the recommended immunization schedule

The infants were classified based on their compliance with the recommended schedule [4].

We calculated compliance at each vaccination moment of the primary series separately, and we calculated full compliance with all three vaccinations. Infants complied with the schedule if they received the first vaccination between 6 and 9 weeks of age, the second vaccination between 2 and 6 weeks (i.e. a 4-week interval with a 14-day window before and after) after the first vaccination and the third vaccination between 2 and 6 weeks after the second vaccination. It is recommended that preterm and low birth weight infants be vaccinated according to standard guidelines, without correction for gestational age. The first vaccination can be administered between 4 and 6 weeks in specific situations, e.g. due to an outbreak or a journey to a country at risk for these diseases. Therefore, we also assessed how many infants received their first vaccination between 4 and 6 weeks of age.

In the northern part of the Netherlands (Groningen and Friesland), the infectious disease control and CHC of the public health services work closely together around pertussis notifications. The infectious disease control department informs the CHC in case of a new pertussis case. Subsequently, CHC offers children, living in the same neighbourhood or village as this pertussis case, their first vaccination as early as possible, from 4 weeks of age. This policy continues until 6 weeks after the last pertussis notification.

Determinants of compliance

We examined the following determinants of compliance with the recommended immunization schedule: gender, year of birth, country of birth of parents, GA, BW, small for gestational age (SGA), executive organization, SES, urbanization rate and public health service region.

Country of birth of the parents was classified into 12 groups: both parents born in the Netherlands, both parents born in Morocco, Netherlands Antilles, Surinam, Turkey or other countries or one parent born in the Netherlands combined with the other parent born in Morocco, Netherlands Antilles, Surinam, Turkey or other countries. We selected these four countries, because they are the most common non-Western ethnicities in the Netherlands.

We excluded infants with a GA of <175 (25 weeks) or >304 days (43.3 weeks) due to the absence of reference BW norms for these GA values. We excluded unrealistic values for BW relative to GA. We removed all observations outside the mean BW ±4 times the standard deviation for the corresponding GA in weeks, for boys and girls separately. We classified GA in three groups: extreme preterm with GA <32 weeks, preterm with GA between 32 and 36 weeks and full-term with GA ≥37 weeks. BW was categorized into extremely low BW (<1000 g), very low BW (1000–1499 g), low BW (1500–2499 g) and normal BW (≥2500 g). Furthermore, when BW was in the lowest 10% values according to Dutch reference norms (taking into account their GA and sex), an infant was considered being SGA.

The executive organization was categorized into three groups: (1) hospital, which includes that all three vaccinations were administered in a hospital; (2) other than hospital, when none of the vaccinations were administered in a hospital but in general by CHC (standard practice) and (3) combination hospital-other, which includes that some vaccinations were administered in a hospital and some elsewhere (CHC, etc.).

Statistical analyses

Median age and 25th and 75th percentiles at the first, second and third DTaP-IPV vaccination were calculated for each year of birth, to examine age at vaccination over time. We calculated the proportions of infants that fully complied with the recommended schedule for the primary series by categories of the determinants. We used Pearson's chi-squared test to check for statistically significant associations between compliance and the determinants.

Table 1 Number of infants and median age at vaccination in days with 25–75 percentiles, per vaccination by year of birth

Birth cohort	Vaccination 1		Vaccination 2		Vaccination 3	
	Total *n* infants vaccinated	Median age in days (25–75 percentiles)	Total *n* infants vaccinated	Median age in days (25–75 percentiles)	Total *n* infants vaccinated	Median age in days (25–75 percentiles)
2007	176,296	63 (59–68)	175,879	97 (91–105)	175,454	132 (124–143)
2008	180,041	62 (58–67)	179,633	96 (90–104)	179,234	130 (122–141)
2009	180,143	62 (58–67)	179,729	95 (90–104)	179,330	130 (122–141)
2010	179,365	62 (57–66)	179,099	95 (89–103)	178,698	130 (122–140)
2011	175,013	61 (57–66)	174,725	95 (89–102)	174,302	129 (122–140)
2012	170,720	60 (56–65)	170,268	93 (87–100)	169,640	127 (120–137)

Moreover, we performed univariable (total study population) and multivariable (complete case analysis) log-binomial regression analyses, yielding prevalence ratios (PRs), on compliance with the recommended schedule. In contrast to the other analyses, we classified country of birth of the parents into three categories for the log-binomial regression: both parents born in Western countries, both parents born in non-Western countries and one parent born in a non-Western country and one parent born in a Western country. A p value <0.05 was considered statistically significant. All analyses were performed using SPSS 19.0.

Results

Study population

The study population included 1,061,578 infants born between 2007 and 2012 who received at least one DTaP-IPV vaccination (which is 97.0–97.5% of all live born children in the Netherlands between 2007 and 2012). Of these 1,061,578 infants, 1,056,658 infants had received at least three vaccinations (99.5%) at a maximum age of 7 years. Over the years, the median age at first DTaP-IPV vaccination decreased from 63 days in 2007 to 60 days in 2012 (Table 1). This trend was also seen for the second (97 days in 2007 to 93 days in 2012) and third vaccination (132 days in 2007 to 127 days in 2012).

Compliance with the recommended schedule

Of the total study population, 866,252 infants (81.6%) received their first vaccination between 6 and 9 weeks; 18,164 infants (1.7%) received their first vaccination before 6 weeks and 177,162 infants (16.7%) after 9 weeks of age (Fig. 1). A total of 937,532 infants (88.3%) received their second vaccination between 2 and 6 weeks after the first vaccination, and 893,972 infants (84.2%) received their third vaccination between 2 and 6 weeks after the second vaccination. In total, 777,887 (73.7%) infants received their first vaccination between 6 and 9 weeks and their second vaccination 2 to 6 weeks later. In total, 684,819 (64.5%) of all vaccinated infants fully followed the recommended immunization schedule for the primary series. Infants who received their first vaccination after 9 weeks of age were more likely to receive their second vaccination more than 6 weeks after their first vaccination than infants who received their first vaccination between 6 and 9 weeks of age (Fig. 1; 17.7 vs 10.2%, $p < 0.001$). Also, infants who received their second vaccination more than 6 weeks after their first vaccination were more likely to receive their third vaccination more than 6 weeks after their second vaccination than infants that received their second vaccination within the recommended interval (30.3 vs 13.4%, $p < 0.001$). However, still the majority of infants that received their first vaccination before 6 weeks or after 9 weeks received their second and third vaccination according to the recommended schedule (13,027/18,164 = 71.7% and 112,820/177,162 = 63.7%, respectively).

The proportion of infants fully complying with the recommended schedule for the primary series increased over time, varying from 60.1% for year of birth 2007 to 68.5% for year of birth 2012 (Table 2). Having parents who were born in the Netherlands was associated with the highest proportion of full compliance (66.8%). The lowest full compliance was seen in infants whose parents were both born in Morocco (56.1%).

Full compliance was higher for full term compared to preterm and extreme preterm infants (65.9 vs 60.2 and 51.9% respectively). This pattern was also observed among infants with an extremely low, very low and low BW compared to a normal BW (43.5, 53.3 and 60.6 vs 66.0%, respectively).

The percentage of infants that followed the schedule fully was higher when they received all vaccinations in a hospital (69.5%) compared to receiving all vaccinations at other organizations (e.g. a CHC) (67.5%) or receiving their vaccinations at both a hospital and another organization (62.2%). A higher proportion of infants living in a municipality with a high average SES (68.6%) was fully vaccinated according to the recommended schedule compared to infants with a low SES at municipality level (59.5%). Infants living in a very low or very

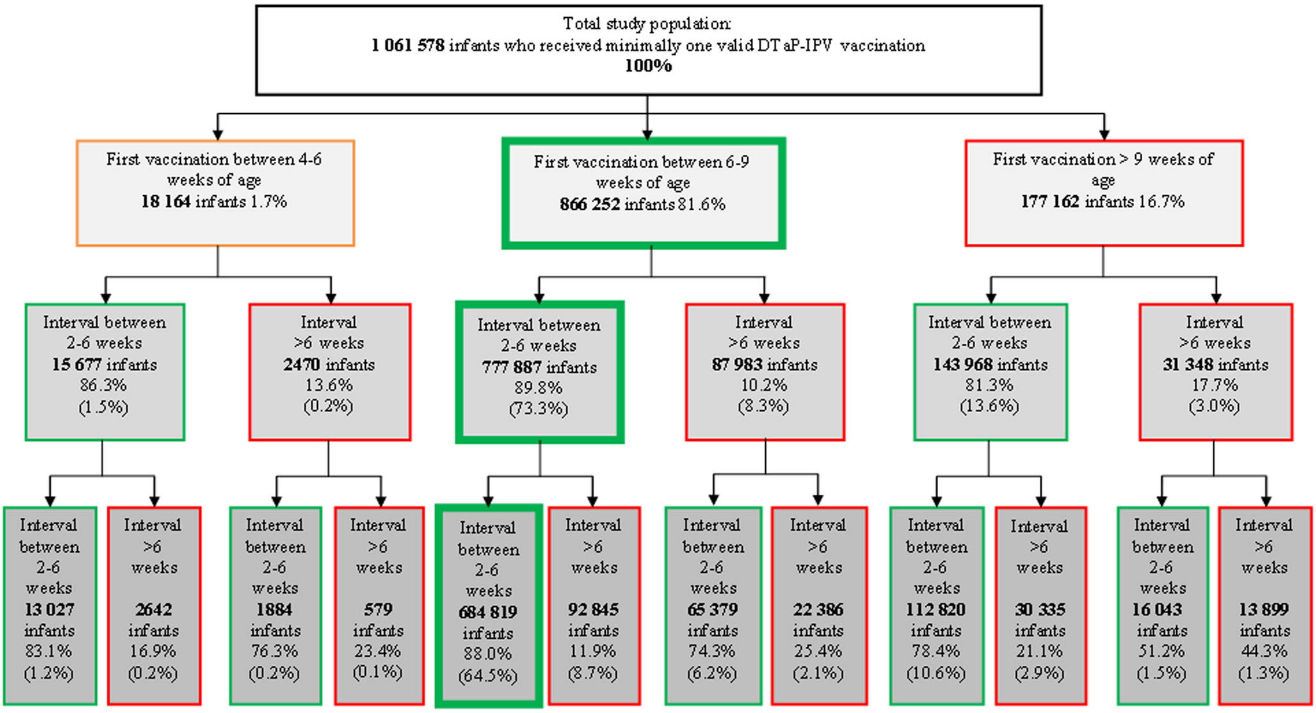

Fig. 1 Flow chart of infants in the study population according to timeliness of the first, second and third DTaP-IPV vaccination. *Light grey boxes* represent the first vaccination, *darker grey boxes* represent the interval between first and second vaccination and *darkest grey boxes* represent the interval between second and third vaccination. *Green border* represents 'according to recommended schedule', *red border* represents 'not according to recommended schedule, *orange border* represents 'partly according to recommended schedule'. The *three boxes with the thick green border* represent the fully recommended schedule. *Percentages* represent number of infants in that *box* divided by number of infants in the *precedent box*. *Percentages in brackets* represent number of infants in that *box* divided by the total study population (n = 1,061,578). Percentages do not always add up to 100% because not all infants received a second (n = 2245) or third vaccination (n = 2675)

high urbanized municipality were less likely to be vaccinated according to the recommended schedule (62.1 and 60.4%, respectively) compared to low, moderately high and high urbanized municipalities (65.3, 67.5 and 65.8%, respectively).

The percentage of infants complying with the recommended schedule varied between the different public health service regions ranging from 49.1 to 77.5%; the highest compliance was found in the southern part of the Netherlands. Over the years 2007 to 2012, the compliance with the recommended schedule increased in the different public health service regions (Fig. 2).

All associations between the determinants and the full compliance were statistically significant.

Multivariable analysis (Table 2) showed a relative increase of 14% in compliance with the recommended schedule from 2007 to 2012 (PR = 1.14 (95% CI 1.13–1.14)). Extreme preterm infants had a relative decrease of 8% in full compliance compared to full-term infants (PR = 0.92 (95% CI 0.89–0.94)). Full compliance was 27% lower in infants with extremely low BW as compared to infants with normal BW (PR = 0.73 (95% CI 0.69–0.78)). Compared to the univariable analysis, the prevalence ratios in the multivariable analysis changed ≥10% for GA, BW and low SES. The effect of GA independent of the other variables in the model became smaller in the multivariable analysis. The independent effect of SES became closer to one in the multivariable analysis (PR = 0.97 (95% CI 0.97–0.98)) compared to the univariable analysis (PR = 0.88 (95% CI 0.86–0.87)). In the multivariable analysis, all associations between the determinants and the compliance stayed statistically significant.

First DTaP-IPV vaccination before 6 weeks of age

In total, 18,164 (1.7%) infants received their first vaccination between 4 and 6 weeks of age (Fig. 1). The proportion of infants that started earlier than 6 weeks of age increased to 3.6% in 2012 compared to 1.0–1.7% in 2007–2011. Almost all public health service regions had the same proportion of infants that received the first vaccination earlier ranging from 0.2 to 0.5% except for regions in the northern part of the Netherlands. Compliance to the full recommended schedule was relatively low in the northern regions because of an earlier administration of the first vaccination (Fig. 3a). However, when including infants who received their first vaccination between 4 and 6 weeks of age as well, the full compliance with the recommended schedule in the northern regions was comparable to the rest of the Netherlands (Fig. 3b).

Table 2 Full compliance with the recommended immunization schedule for the primary series and potential determinants with corresponding prevalence ratio and 95% confidence intervals as determined by univariable and multivariable log-binomial regression analyses

	n vaccinated with full recommended schedule (%)	Univariable analysis		Multivariable analysis	
		Prevalence ratio	95% CI	Prevalence ratio	95% CI
Total	684,819 (64.5)				
Gender					
Male (ref)	348,807 (64.2)	–	–	–	–
Female	336,012 (64.8)	1.01	(1.01–1.01)	1.01	(1.01–1.01)
Year of birth					
2007 (ref)	105,956 (60.1)	–	–	–	–
2008	113,836 (63.2)	1.05	(1.05–1.06)	1.05	(1.05–1.06)
2009	114,583 (63.6)	1.06	(1.05–1.06)	1.05	(1.05–1.06)
2010	116,162 (64.8)	1.08	(1.07–1.08)	1.07	(1.07–1.08)
2011	117,332 (67.0)	1.12	(1.11–1.12)	1.10	(1.10–1.11)
2012	116,950 (68.5)	1.14	(1.13–1.15)	1.14	(1.13–1.14)
Country of birth of parents					
Western–Western (ref)	558,592 (66.2)	–	–	–	–
Non-Western–Western	51,181 (61.3)	0.93	(0.92–0.93)	0.95	(0.95–0.96)
Non-Western–non-Western	51,980 (58.1)	0.88	(0.87–0.88)	0.92	(0.91–0.92)
Missing	23,066				
Gestational age (GA)					
Extreme preterm	4553 (51.9)	0.79	(0.77–0.80)	0.92	(0.89–0.94)
Preterm	22,509 (60.2)	0.91	(0.91–0.92)	0.95	(0.94–0.96)
Full term (ref)	651,530 (65.9)	–	–	–	–
Missing	6227				
Birth weight (BW)					
Extremely low	826 (43.5)	0.66	(0.63–0.69)	0.73	(0.69–0.78)
Very low	2971 (53.3)	0.81	(0.79–0.83)	0.88	(0.85–0.91)
Low	31,028 (60.6)	0.92	(0.91–0.93)	0.95	(0.94–0.95)
Normal (ref)	643,767 (66.0)	–	–	–	–
Missing	6227				
Small for gestational age (SGA)					
SGA	43,284 (64.8)	0.99	(0.98–0.99)	1.01	(1.01–1.02)
Not SGA (ref)	635,308 (65.7)	–	–	–	–
Missing	6227				
Executive organization					
Other than hospital (ref)	515,204 (67.5)	–	–	–	–
Hospital	8933 (69.5)	1.03	(1.02–1.04)	0.98	(0.97–0.99)
Combination hospital-other	139,303 (62.2)	0.92	(0.92–0.92)	0.96	(0.96–0.97)
Missing	21,379				
Socioeconomic status (SES)—municipality level					
High SES (ref)	68,196 (68.6)	-		-	
Average SES	458,912 (65.8)	0.96	(0.96–0.96)	0.99	(0.98–0.99)
Low SES	157,678 (59.5)	0.88	(0.86–0.87)	0.97	(0.97–0.98)
Missing	54				
Urbanization rate—municipality level					
Very high (ref)	140,374 (60.4)	–	–	–	–
High	193,844 (65.8)	1.09	(1.09–1.09)	1.10	(1.09–1.11)
Moderately high	147,479 (67.5)	1.12	(1.11–1.12)	1.10	(1.09–1.11)
Low	141,042 (65.3)	1.08	(1.08–1.09)	1.10	(1.09–1.11)
Very low	62,047 (62.1)	1.03	(1.02–1.03)	1.06	(1.05–1.07)
Missing	33				
Public health service region					
GGD Amsterdam (ref)	40,524 (61.2)	–	–	–	–
GGD Brabant-Zuidoost	27,713 (61.3)	1.00	(0.99–1.01)	0.87	0.86–0.88
GGD Drenthe	18,401 (62.7)	1.03	(1.01–1.04)	0.90	0.89–0.91
GGD Flevoland	18,288 (60.2)	0.98	(0.97–1.00)	0.87	0.86–0.88
GGD Fryslân	21,503 (52.1)	0.85	(0.84–0.86)	0.74	0.73–0.75
GGD Gelderland-Zuid	20,873 (64.6)	1.06	(1.05–1.07)	0.93	0.92–0.94
GGD Gooi en Vechtstreek	9699 (62.6)	1.02	(1.01–1.04)	0.90	0.90–0.91
GGD Groningen	16,320 (49.1)	0.80	(0.79–0.81)	0.72	0.72–0.73
GGD Haaglanden	46,972 (65.7)	1.07	(1.07–1.08)	1.03	1.03–1.04
GGD Hart voor Brabant	47,775 (74.7)	1.22	(1.21–1.23)	1.07	1.06–1.08
GGD Hollands Midden	32,548 (65.9)	1.08	(1.07–1.09)	0.94	0.93–0.95
GGD Hollands Noorden	27,059 (67.6)	1.11	(1.10–1.12)	0.96	0.96–0.97
GGD IJsselland	24,396 (67.6)	1.11	(1.10–1.12)	0.96	0.96–0.97
GGD Kennemerland	25,287 (72.6)	1.19	(1.18–1.20)	1.07	1.06–1.08
GGD Limburg Noord	19,907 (71.8)	1.18	(1.16–1.19)	1.03	1.02–1.04
GGD Noord- en Oost-Gelderland	31,110 (64.5)	1.05	(1.05–1.06)	0.92	0.91–0.92
GGD Regio Utrecht	57,702 (65.5)	1.07	(1.06–1.08)	0.95	0.94–0.95
GGD Rotterdam-Rijnmond	50,416 (60.0)	0.98	(0.97–0.99)	0.94	0.93–0.94
GGD Twente	24,620 (61.0)	1.00	(0.99–1.01)	0.87	0.86–0.88
GGD West-Brabant	29,416 (70.9)	1.16	(1.15–1.17)	1.01	1.00–1.01
GGD Zaanstreek/Waterland	12,911 (63.9)	1.05	(1.03–1.06)	0.90	0.89–0.91

Table 2 (continued)

	n vaccinated with full recommended schedule (%)	Univariable analysis		Multivariable analysis	
		Prevalence ratio	95% CI	Prevalence ratio	95% CI
GGD Zeeland	13,630 (64.6)	1.06	(1.05–1.07)	0.93	0.92–0.94
GGD Zuid-Holland Zuid	20,989 (66.9)	1.09	(1.08–1.11)	0.95	0.94–0.96
GGD Zuid-Limburg	21,454 (77.5)	1.27	(1.26–1.28)	1.11	1.10–1.12
Hulpverlening Gelderland-Midden	25,273 (60.3)	0.99	(0.98–0.99)	0.86	0.86–0.87
Missing	33				

Discussion

In total, 81.6% of all vaccinated infants in 2007–2012 received their first DTaP-IPV vaccination on time between 6 and 9 weeks after birth. Thus, 18.4% of the first vaccination was not given according to the recommended schedule, either due to an earlier (1.7%) or later start (16.7%). Most of these infants received their second and third vaccination in accordance with the recommended schedule. However, if the first and/or second vaccination were not according to the recommended schedule, it was also more likely that the second or third vaccination was not received according to the recommended schedule. In total, 64.5% of the infants complied with the recommended schedule for the full primary series. Prematurity, low birth weight and having parents not born in the Netherlands were determinants of less full compliance with the recommended schedule. Furthermore, there were geographical differences in full compliance.

If the first vaccination was delayed, we observed that the second vaccination was not given earlier to 'catch up' with the schedule. Therefore, a delayed administration of the first dose resulted in a higher age at second and third vaccination as well. Moreover, if the first vaccination was delayed, there was even a higher chance that the following vaccinations were administered 'out-of-schedule' as well, resulting in even a higher age at second and third vaccination. These delays

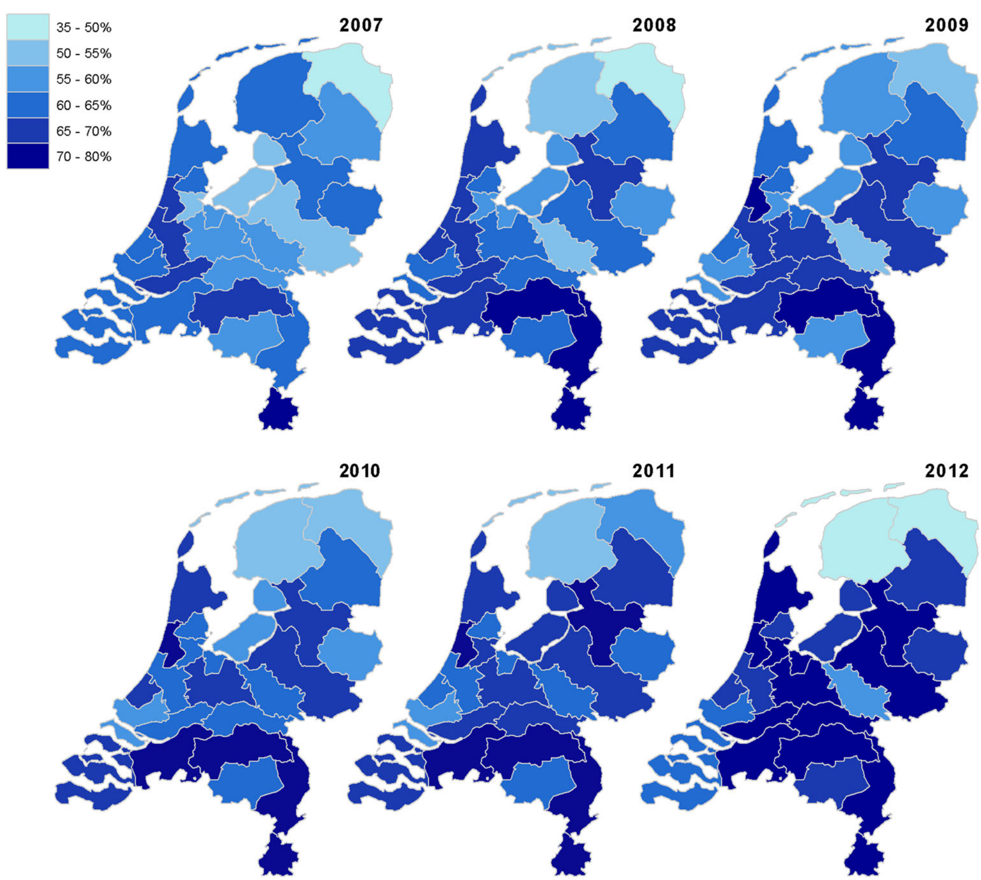

Fig. 2 Compliance with the recommended schedule (in proportions) over the years 2007 to 2012 by the public health service region

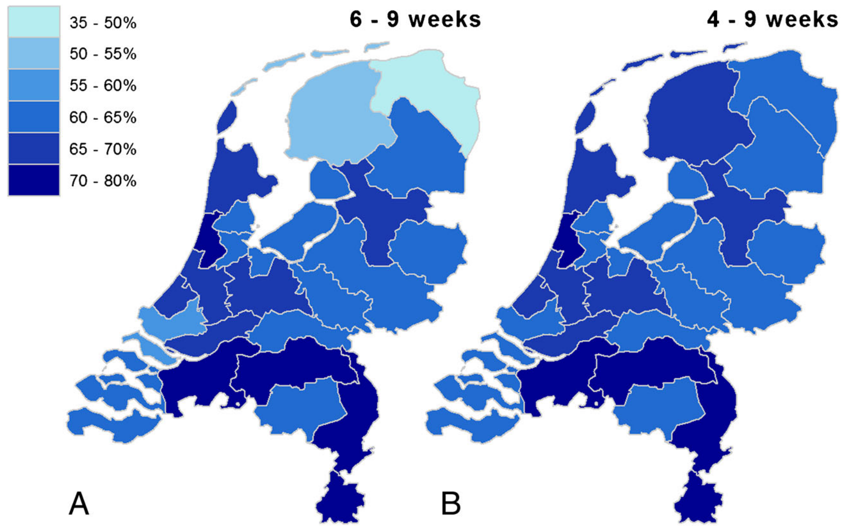

Fig. 3 Compliance with the recommended schedule when first vaccination was received between 6 and 9 weeks (**a**) and between 4 and 9 weeks (**b**) of age by public health service region for the years 2007 to 2012 combined

resulted in a longer period at risk for, e.g. pertussis, which is endemic in the Netherlands. Several studies have shown that even one DTaP vaccination has an effect on preventing pertussis and that vaccination delays lead to more cases [7, 17]. Glanz et al. [7] concluded that under-vaccination with DTaP vaccine increased the risk of pertussis among infants 3 to 36 months of age. Under-vaccination was defined as the number of doses of DTaP vaccine that was either missing or delayed by the index date.

Although the risk of (pertussis) infection is higher with a delayed schedule due to a longer time period without protection, longer intervals may lead to higher antibody levels. Already a long time ago, Brown et al. [3] examined different schedules among infants between 3 and 7 months of age, varying age at first DTP-IPV vaccination and interval between doses. They concluded that the longer intervals between doses yielded higher antibody levels to all the components of the vaccine, when using a 2-month interval instead of 1-month interval. Spijkerman et al. [20] also showed that delaying the first vaccination (2 to 3 months) and using longer intervals between vaccinations (2 months instead of 1 month) of 13-valent pneumococcal conjugate vaccine (PCV13) resulted in higher pneumococcal antibody levels. Assuming that higher antibody levels give higher protection levels, this means that deciding on timing of vaccinations is a trade-off between early protection and higher protection levels. As is shown by the large variation in immunization schedules across Europe, this trade-off depends on the epidemic situation in different countries and probably also on other historical and social perspectives.

Our results show that full compliance with the recommended schedule increased over the years (from 60.1% in 2007 to 68.5% in 2012). This is probably the result of interventions to improve timeliness of the first DTaP-IPV vaccination in the Netherlands [12], for example, promoting awareness of the importance of a timely administration when planning the consults, planning two follow-up appointments instead of one and the administration of the first vaccination during an earlier consult when the child is already old enough. We observed a higher proportion of infants vaccinated before 6 weeks of age in 2012 due to the rise in pertussis cases in the first half year of 2012 in the Netherlands [14]. Due to this rise, it was advised to vaccinate infants as soon as possible hence the regional differences [16]. The increase in compliance with the recommended schedule raises the question whether this influenced disease epidemiology. However, as the incidence of the diseases which we vaccinate against is very low among infants (<5 cases per year) [19], except for pertussis, it is not possible to look at a trend over time for these diseases and to correlate it to compliance. For pertussis, an increase in notifications among 0-year olds was actually seen in 2012, so no correlation was present between compliance with the immunization schedule and pertussis incidence. However, many other factors than compliance with the immunization schedule will have influenced pertussis epidemiology.

This study is an extension to the study by Woestenberg et al. [24] who found that prematurity, low birth weight, having parents who are born outside of the Netherlands, a low SES in municipality and a very low urbanization rate were related to a delay in first vaccination for children born between 2006 and 2010 in the Netherlands. We found the same factors determining compliance with the full schedule of the primary series. This is of course partly due to the relation with timing of the first vaccination, but we found that the same determinants were also related to the interval between the first and second and the second and third vaccination. Therefore, besides a delayed start, the above-mentioned determinants were also related to less full compliance with the immunization schedule because of a longer interval between vaccinations than was recommended.

The strength of our study is that we used a nationwide study population registered in Præventis, which included virtually all newborns in the Netherlands because it is linked to the population register. Furthermore, it provided almost complete information on important characteristics such as country of birth of parents, birth weight, gestational age and executive organization. This is the best tool for assessing long-term performance of the immunization program [13]. The study also has some limitations. First, we were limited in the characteristics available in Præventis for studying association with compliance. Several studies showed other variables to be associated with timeliness of vaccinations including family size, marital status of mother, birth order, family income, belief of parents and health status of the infant [2, 6, 10]. These characteristics were not available, but would have been of interest. Moreover, qualitative research could be an addition to discover the parent's motives to comply (or not) with the recommended schedule. Second, urbanization rate and SES were based on last known municipality, which could differ from the actual place of residence at vaccination due to recent moves. Nevertheless, we suspect that the proportion of moves to another municipality is small and thus will have a minimal impact on the results. Finally, the recommended interval between the first and second and the second and third vaccination is 4 weeks but a permitted window around these 4 weeks is not explicitly defined. We used a 14-day window before and after vaccination for both intervals, which is an arbitrary choice. A shorter or longer window will obviously influence the proportion of compliance. However, when using a longer window (2–9 weeks), we found that the effect of the determinants on compliance stayed the same.

In conclusion, our study showed that incomplete compliance with the recommended schedule for the primary series is associated with prematurity, extremely or very low BW and non-Western country of birth of parents mainly not only because of a delay in the first vaccination but also because of a longer interval between vaccinations. As a consequence, infants with a delayed first vaccination and/or delayed interval between vaccinations are at increased risk of vaccine-preventable diseases, such as pertussis. Although a high proportion of Dutch infants received their first vaccination on time, the timeliness of the Dutch NIP can be further improved. Knowledge about the timing of the recommended immunization schedule amassed through this study is a starting point for further research on the effects of immunization schedules on antibody levels and qualitative research to evaluate the Dutch NIP.

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Authors' contributions This study was initiated by HdM and MK. Data analyses were conducted by ES under coordination of MK and AvL. ID, GB and NvdM assisted in interpretation of the data and results. ES drafted the manuscript. AvL, ID, GB, NvdM, HdM, and MK critically revised the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The manuscript does not contain clinical studies or patient data. Anonymous data from a healthcare registration were used. For this type of study, formal consent is not required.

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