Vaccine 37 (2019) 5862–5867

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Timeliness of immunisations in preterm infants in the Netherlands

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ARTICLE INFO

Article history:
Received 19 April 2019
Received in revised form 1 August 2019
Accepted 7 August 2019
Available online 20 August 2019

Keywords:
Preterm infants
Timeliness
Vaccination
National immunisation programme

ABSTRACT

Background: In the Netherlands, preterm infants receive the immunisations at the same chronological age as recommended for term infants without correction for gestational age (GA). The aim of this paper was to describe the timeliness of the routine Dutch national immunisation schedule in preterm infants in their first year of life and to evaluate possible determinants of delay.

Methods: Preterm infants were prospectively recruited between October 2015 and October 2017 and stratified according to GA (<28, 28–32 and 32–36 weeks). Data from the baseline parental questionnaire, monthly parental questionnaires and medical records were used to determine the immunisation age and proportion of infants timely receiving the first immunisations (between 42 and 63 days). Results were compared between the GA and birth weight (BW) groups. Determinants associated with timeliness of immunisation were studied by multivariate logistic regression analysis.

Results: Timely start of immunisation occurs in 60.5% of preterm infants in the Netherlands. The proportion of infants receiving the first immunisation on time was lowest for the group with GA <28 weeks (37%). The mean age of the first immunisation across all GA groups was 62.7 days (range 33–118) and differed significantly between GA group <28 weeks and the other two GA groups of 28–32 and 32–36 weeks ($p < 0.001$). Similar results were seen when stratified by BW. Multivariate analysis showed that low socioeconomic status (SES) and prolonged hospitalisation beyond 37 weeks each negatively influenced timeliness of the first immunisation.

Conclusion: These findings indicate that start of immunisations was often delayed in prematures and differs for different GA groups, being lowest (37%) in infants <28 weeks GA. Lower SES and prolonged hospital stay beyond 37 weeks GA are important determinants of timeliness. Efforts to improve timeliness should focus most on counselling parents in lower SES.

1. Introduction

In the Netherlands, the proportion of preterm (<37 weeks gestation) and very preterm (<32 weeks gestation) births amount to approximately 7% and 1.5% of the Dutch birth cohort, respectively, corresponding to roughly 12,000 and 2500 births annually [1]. Preterm infants receive vaccinations at the same chronological age as recommended for term infants without correction for gestational age (GA) [2,3]. The schedule for the Dutch national immunisation programme (NIP) starts with DTaP-IPV-Hib-HepB (diphtheria, tetanus, acellular pertussis, inactivated polio, Haemophilus influenzae type b and hepatitis B) in a 3+1 dose schedule at 6–9 weeks, 3, 4 and 11 months and pneumococcal conjugate vaccine (PCV10) in a 2+1 dose schedule at 6–9 weeks, 4 and 11 months of age [2].

Preterm birth is associated with an increased susceptibility to infections due to immunological immaturity and decreased

Abbreviations: BW, birth weight; DTaP-IPV-Hib-HepB, diphtheria, tetanus, acellular pertussis, inactivated polio, Hib, Hep B; GA, gestational age; Hep B, hepatitis B; Hib, haemophilus influenzae type b disease; NIP, national immunisation programme; PCV, pneumococcal conjugate vaccine; SES, socioeconomic status.

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https://doi.org/10.1016/j.vaccine.2019.08.006
0264-410X/

transfer of maternal antibodies [4,5]. The rate of maternal immunoglobulin (IgG) antibody transfer increases with duration of gestation and peaks in the second half of the third trimester of pregnancy [4,6–8]. Therefore, infants born prematurely have lower levels of protective maternal antibodies [5,9,10]. Particularly, the risk of severe pertussis and pneumococcal disease is increased in preterm infants in the first months of life compared with term infants [11–13]. Regular epidemics of pertussis, which tend to occur every three years in the Netherlands, therefore pose an increased risk to preterm infants and timely immunization is essential for protection [14,15].

An earlier study in the Netherlands described that 25% of preterm infants did not receive their primary immunisations on time [16]. Since then, several changes have been made to the Dutch NIP schedule but it is unknown if this has influenced timeliness of vaccination among preterm infants. In 2011 Hep B was added to the Dutch NIP and the 7-valent pneumococcal conjugate vaccine (PCV) was replaced by the 10-valent PCV. In 2013 the PCV10 schedule was changed from 3+1 to a 2+1 dose-schedule [2].

Delayed start of immunisations in preterm infants has also been reported in other countries, for example Italy, the USA and Switzerland [9,17–20]. Importantly, factors that may influence timeliness, such as gestational age (GA) of the infant, socioeconomic factors or hospital stay were not systematically evaluated, while such characterization may help define target groups for focused efforts to improve timeliness. The aim of this paper was to describe the timeliness of the routine Dutch national immunisation schedule in preterm infants in their first year of life and to evaluate possible determinants of delay.

2. Methods

2.1. Study design and participants

This study is part of a prospective cohort study evaluating the immunological protection against vaccine preventable disease by the routine national immunisation programme (NIP) in preterm infants in the Netherlands. Between October 2015 and November 2017, preterm infants were recruited before start of immunisations at eight Dutch hospitals, including five centres hosting neonatal intensive care units (NICU) and three general hospitals with a neonatal high care unit.

All preterm infants (GA $\leq$ 36 weeks) were eligible for study enrolment. Written informed consent was obtained from both parents or guardians of infants before enrolment. Ethical approval was obtained from the Medical Ethical Committee of the University Medical Centre Utrecht. This study was designed and conducted in accordance with the Good Clinical Practice guidelines established by the International Conference on Harmonisation and with the Declaration of Helsinki. This study was registered at the Netherlands Trial Register (NL7142).

2.2. Data collection

A timeline of the data collection is presented in Fig. 1. Information on pregnancy, delivery and duration of hospitalisation as well as socioeconomic status (SES) based on education level, family housing situation and ethnicity was collected at a postnatal age of six weeks by a baseline parental questionnaire. Additional information was extracted from medical records by hospital staff at age of 6 weeks and 5 months and included diagnoses of congenital or perinatal disorders, data on hospital stay including duration, supportive therapies, medical complications and treatment interventions (e.g. medication, surgery). Follow-up included monthly parental questionnaires up to 1 year of age collecting information on upper respiratory tract infections, rehospitalisation's, reasons for rehospitalisation's, type and dates of immunisations and immunisation side-effects.

Immunisation dates provided by the parents were checked with dates recorded in the immunisation certificate during home visits.

2.3. Definitions

Infants received the immunisations as per normal practice and in accordance with the Dutch national immunisation programme (NIP). Participation in the study had no influence on the timing of vaccine administration. According to the regular Dutch NIP, the first DTaP-IPV-Hib-HepB combination vaccine and PCV10 should be administered between 6 and 9 weeks (42 and 63 days) of postnatal age both for preterm and term infants. The second and third dose of the primary series should be given at 28 ± 14 days intervals, which corresponds to ages 56–105 days for the second and 70–147 days for the third immunisation [2].

The booster immunisation should be administered preferably six months (182 days) after the third dose of the primary series. When the booster is administered within four months (121 days) after the last vaccination of the primary series, this is considered too early and therefore possibly insufficiently protective. The Dutch guideline does not explicitly define an upper age-limit for administration of the booster dose, but we considered administration more than eight

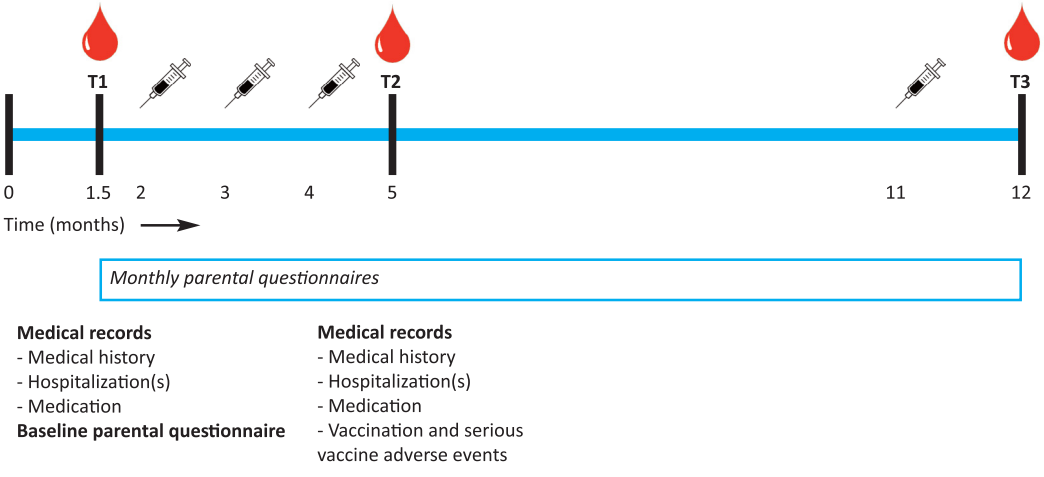

Fig. 1. Time-line of data collection and immunisations.

months (>243 days) after completion of the primary series to be outside the recommended schedule [2].

SES was based on parents' educational level which was categorized as either high (higher vocational education or university degree) or regular (all other education levels) for each parent separately. Next, SES for the infant was classified into three different categories: 'high' when both parents were highly educated; 'intermediate' when one parent was highly educated and the one regular educated; and 'regular' when both parents were regular educated.

Ethnicity was based on parental country of birth and classified into three categories: both parents born in European countries [21], both parents born in non-European countries and one parent born in a non-European country and one parent born in a European country.

2.4. Outcomes

The primary endpoint was timeliness of the first immunisation, defined as the first dose of the primary series administered between 42 and 63 days of postnatal age.

Secondary outcomes included appropriate timing of second, third and booster dose, as described above and completion of the complete primary series according to recommended timing.

2.5. Statistical analysis

For each participant, timing of each immunisation was calculated based on postnatal age, without correction for GA and classified as either (1) on time (i.e. within the appropriate age-window), (2) too early or (3) too late. Preterm infants were stratified based on GA into three groups: <28 weeks, 28–32 weeks and 32–36 weeks or, based on birth weight (BW) into four groups: <1000, 1000–1499, 1500–2499 and ≥2500 g.

The proportion of infants that received their first and booster vaccination on time was calculated for the full study cohort and separately by GA and BW groups. Similarly, proportions of infants that fully complied with the recommended timing for the primary series were calculated. Next, the mean postnatal age per vaccine dose and per GA and BW was calculated. Cases with a missing date for the first immunisation were excluded from the analysis.

To study possible determinants of timeliness, the following variables were considered and assessed univariately for an association with receiving the first immunisation on time: GA, gender, ethnicity, SES, multiple-birth gestation and postnatal length of stay in hospital. Pearson's chi-square test was used for categorical variables and t-tests for linear variables. Univariate determinants with a p-value < 0.1 were included in the multivariate logistic regression analysis. A p-value < 0.05 was considered statistically significant. All analyses were performed using SPSS 24.0.

3. Results

3.1. Characteristics of study population

In total, 296 preterm infants were enrolled in this study (Fig. 2). Twenty infants were excluded from analysis due to missing data on the first immunisation date. The final analysis included 276 infants,

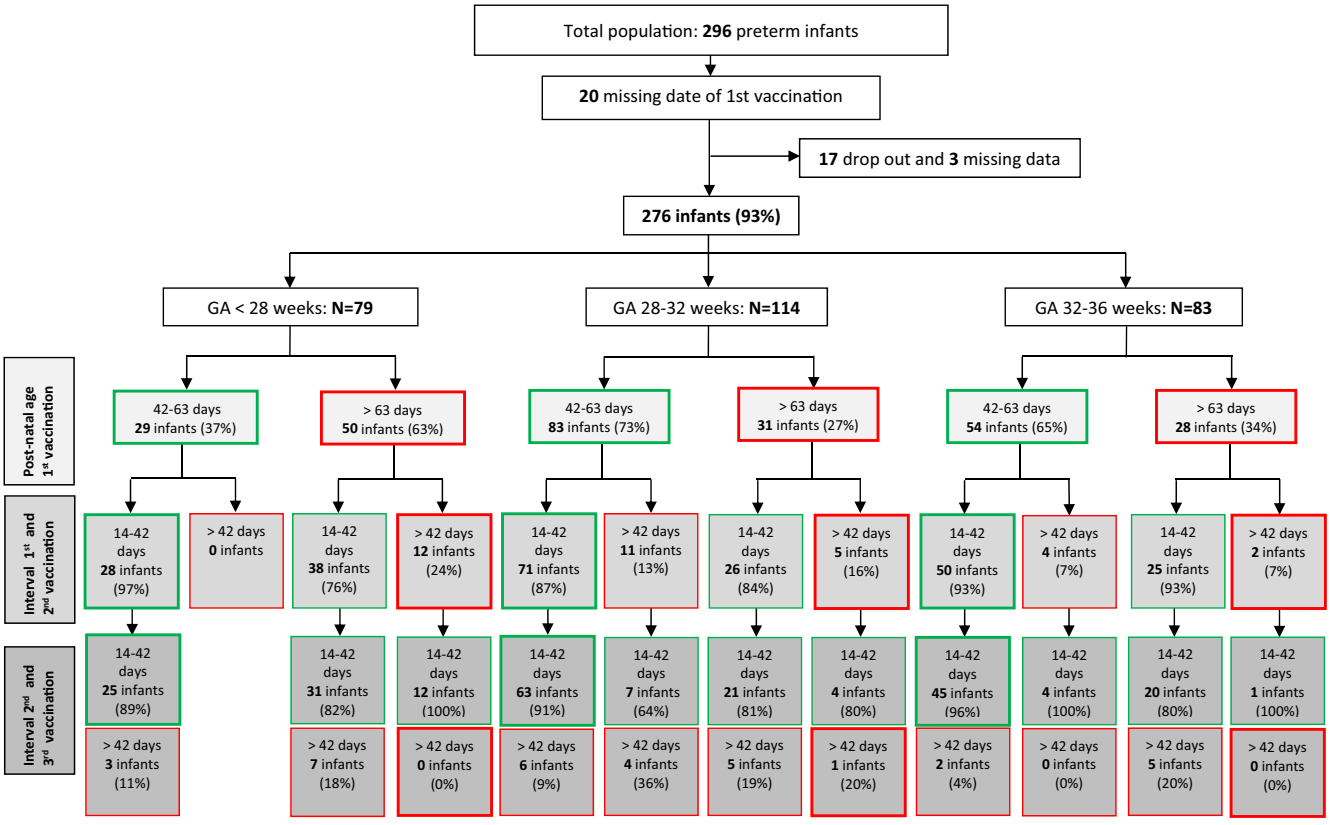

Fig. 2. Flowchart of infants in the study population divided in different GA groups according to timeliness of first, second and third DTaP-IPV-Hib-HepB and PCV10 vaccination. Light grey boxes represent the first vaccination, darker grey boxes represent the interval between the first and second vaccination, darkest grey boxes represent the interval between the second and third vaccination. The boxes with the thick green border represent the fully recommended schedule per GA group. The boxes with the thick red border represent fully unrecommended schedule per GA group. Percentages represent the number of infants in that box divided by number of infants in precedent box. Percentages do not always add up to 100%, because not of all infants were all vaccine dates complete and infants who received their immunisation too early were left out in this figure. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of whom 155 (56.2%) were male. Of the 276 infants, 79 (29%) had a GA <28 weeks, 114 (41%) between 28 and 32 weeks and 83 (30%) between 32 and 36 weeks. The overall mean GA was 30 weeks + 1 day (Standard Deviation [SD]: ±3 weeks + 1 day), the mean BW was 1420 g (SD: ±563 g) and 98 infants (35.5%) were from multiple-birth (Table 1).

Overall, the mean duration of postnatal hospitalisation was 59.9 days (SD: ±35.6). Shorter duration of hospitalisation occurred with increasing GA: infants with GA <28 weeks stayed on average 101.4 days (SD: ±24.9) in the hospital compared to 61.6 days (SD: ±21.2) for GA-group 28–32 weeks and 27.0 days (SD: ±19.0) for GA-group 32–36 weeks. High SES was classified for 47.1% (n = 130) of parents. For 231 infants (83.7%) both parents were of European origin.

3.2. Timeliness of immunisations

In total, 166 infants (60.1%) received the first immunisation on time between 42 and 63 days (green boxes in Fig. 2, Table 2) whereas in 109 infants (39.5%) the first immunisation was administered delayed (Fig. 2, red boxes). Only one infant was vaccinated too early. The proportion of infants receiving the first immunisation on time was lowest for the group with GA <28 weeks (37%, Fig. 2 and Table 2). Timeliness of first immunisation was not significantly different between infants with GA 28–32 weeks versus GA 32–36 weeks (73% versus 65% respectively, p = 0.30).

The mean age of the first immunisation across all GA groups was 62.7 days (range 33–118) and differed significantly between GA group <28 weeks and the other two GA groups of 28–32 and 32–36 weeks (p < 0.001). Results were comparable when the infants were stratified by BW category (Table 2).

Although the percentage of infants with first immunisation on time varied between 37 and 73%, in the different GA groups the second and third dose were more likely to be administered within the appropriate time window (84–93%) (Table 2).

Overall, in 133 (48.2%) infants, timing of immunisations was compliant with recommendations for the complete primary series (Fig. 2). Stratified by GA-group, these proportions were 32% (n = 25), 55% (N = 63) and 54% (N = 45, Fig. 2).

3.3. Timeliness of the booster immunisation

For the booster dose, higher rates of timeliness were observed (Table 2). Overall, the proportion of infants receiving the booster

Table 1
Baseline-characteristics study population.

	Total N = 276	GA <28 weeks N = 79	GA 28–32 weeks N = 114	GA 32–36 weeks N = 83	P-value
Mean GA (SD) in days	210.7 (21.7)	184.2 (8.2)	209.9 (7.4)	236.9 (8.4)	<0.001
Gender					
Male	155 (56.2%)	53 (67%)	58 (51%)	44 (53%)	
Female	121 (43.8%)	26 (33%)	56 (49%)	39 (47%)	0.07
Ethnicity					
European-European	231 (83.7%)	62 (79%)	94 (83%)	75 (91%)	
European-non-European	21 (7.6%)	8 (10%)	9 (8%)	4 (5%)	0.17
Non-European-non-European	16 (5.8%)	8 (10%)	6 (5%)	2 (2%)	
Socioeconomic status (SES)					
High SES	130 (47.1%)	30 (38%)	59 (52%)	41 (49%)	
Average SES	54 (19.6%)	18 (23%)	19 (17%)	17 (21%)	0.43
Low SES	75 (27.2%)	25 (32%)	28 (24%)	22 (27%)	
Parents living together					
Yes	254 (92.0%)	75 (95%)	99 (87%)	80 (96%)	
No	12 (4.4%)	2 (3%)	10 (9%)	0	0.01
Smoking during pregnancy					
Yes	13 (4.7%)	5 (6%)	7 (6%)	1 (1%)	
No	251 (90.9%)	71 (90%)	101 (89%)	79 (95%)	0.19
Multiple-birth gestation					
Yes	98 (35.5%)	33 (42%)	52 (45%)	13 (16%)	
No	178 (64.5%)	46 (58%)	62 (55%)	70 (84%)	<0.001
Mean duration of hospitalization (SD) in days	59.9 (35.6)	101.4 (24.9)	61.6 (21.2)	27.0 (19.0)	<0.001

Table 2
Number and percentage of infants, mean age at vaccination in days at the first vaccination and proportion vaccination on time (<63 days) according to GA and BW.

	N Vaccinated (% of the population)	Mean age at first vaccination (range)	1st Vaccination on time (%)	2nd vaccination on time (%)	3rd vaccination on time (%)[a]	Booster vaccination on time (%)[b]
Study population	276 (100)	62.7 (33–118)	166 (60)	239 (87)	234 (87)	217 (85)
GA						
GA: <28 weeks	79 (29)	69.2 (49–118)	29 (37)	66 (84)	68 (86)	58 (78)
GA: 28–32 weeks	114 (41)	59.4 (42–117)	83 (73)	97 (86)	95 (86)	90 (85)
GA: 32–36 weeks	83 (30)	61.0 (33–82)	54 (65)	76 (93)	71 (91)	69 (91)
BW						
<1000 g	74 (27)	67.9 (50–118)	27 (37)	64 (88)	59 (83)	52 (78)
1000–1499 g	89 (32)	61.6 (42–117)	62 (70)	72 (81)	77 (87)	73 (85)
1500–2499 g	104 (38)	60.0 (33–87)	71 (68)	95 (91)	91 (91)	85 (89)
≥2500 g	9 (3)	60.3 (50–75)	6 (67)	8 (100)	7 (88)	7 (100)

[a+b] Due to more missing vaccine dates lower number of total vaccinated population.

immunisation on time was 84.8% (N = 217/256) and increased with GA from 78% to 91% for youngest to oldest GA groups. None of the infants received the booster immunisation too early (<121 days). In total 39 (15.2%) infants received the booster too late (>243 days).

3.4. Determinants associated with timeliness

In the univariate analysis, SES, GA and duration of postnatal hospitalisation were significantly associated with timeliness of the first vaccination and therefore included in the multivariate model.

There was a strong inverse correlation between GA and duration of hospitalisation ($\rho = 0.88$) resulting in collinearity. We therefore decided to use hospitalisation beyond GA 37 weeks instead, to assess the additional effect of hospitalisation duration, not mediated through GA. In the multivariate analysis regular SES compared to high SES had an odds ratio (OR) of 2.58 (95% CI: 1.35–4.93, p = 0.004) for timeliness of first vaccination. The OR for a younger GA was 1.08 (95% CI: 0.98–1.20, p = 0.14) per week and for one-week additional hospital stay beyond 37 weeks the OR was 1.13 (95% CI: 1.01–1.26, p = 0.03). The OR for GA was however no longer statistically significant in the multivariate analyses.

4. Discussion

In this comprehensive cohort, spanning preterm infants of all GA groups, we found that 60.1% of infants received the first NIP immunisations on time and that timeliness was lowest for infants with GA < 28 weeks. In this group, only 37% received the first immunisation on time. Despite the differences in the first immunisation date, the timeliness for the 2nd and 3rd immunisation was high (>84%) and similar for all three GA groups. Timeliness of the booster immunisation was also high for the three GA groups, but still lowest for the youngest GA. Stratification by BW revealed similar results. In total, 48.2% of all preterm infants fully complied with the recommended timing for the primary series. Multivariate analysis showed that lower SES and prolonged hospitalisation beyond 37 weeks GA each negatively influenced timeliness of the first immunisation.

Next to an unwanted longer duration of high susceptibility to vaccine preventable diseases after a delayed start of immunisations in preterm infants, immunological immaturity may lead to lower antibody responses after the primary series [5,13]. As these suboptimal antibody concentrations steadily decline to insufficiently protective levels during the months after completion of the primary series, a subsequent delay in administration of the booster dose may create a second age-window of vulnerability. On the other hand, longer intervals between immunisations and a later start will improve antibody levels [22]. Also, a booster immunisation at a more mature age may enhance antibody levels, which favours a delayed booster to achieve better and more sustained protection in the second year of life. The optimal age for a booster dose in preterm infants has not been determined and an upper age-limit for the booster dose is not defined in the Dutch guideline [2]. Apart from delayed start of immunisations, another concerning issue is the decreasing vaccine coverage in the Netherlands. Vaccine coverage for the primary series and booster immunisation in the first year of life was very high in the past (>95%), but slightly decreased over the last 2–3 years to 93% [23]. A continued declining trend may compromise the herd protection for vaccine preventable diseases in the population, which in turn, is most concerning for unimmunized preterm infants [23].

In our study, hospitalisation beyond GA 37 weeks and lower SES were determinants that most strongly affected timeliness of immunisations. How these factors mediate a delay in the start of immunisations in preterm infants was not investigated in this study. We assume that prolonged hospitalisation is a proxy for presence of medical conditions or treatments that (temporarily) contra-indicate immunisations. As this occurs most often in very preterm infants, the delay is also most pronounced in the group with youngest GA. In addition, younger GA itself may negatively influence timeliness, but after correction for prolonged hospital stay, this effect was no longer significant. This seems to indicate that delay in immunisations in preterm infants is primarily because of medical reasons, rather than based on prematurity, at least in the youngest GA groups, but this hypothesis needs to be confirmed. The negative influence of lower SES on timeliness was also reported in the study by Woestenberg et al. [16]. Efforts to improve timeliness through intensified counselling of regular SES parents could therefore be effective. In contrast to previous studies, this study found no effect of ethnicity on immunisation timeliness, possibly due to the low number of non-European parents in this cohort limiting our statistical power to evaluate this [16,24,25].

Other reasons for delaying immunisations in particular in very preterm infants may be concerns among doctors about potentially inadequate immune responses due to immunological immaturity when immunised according to schedule or parental concerns about adverse events [12,26,27]. However, severity and frequency of most vaccine-related adverse events in preterm infants do not differ from term infants [10,26,28]. On the other hand, studies have shown that preterm infants can temporally experience specific adverse events like apnea and bradycardia after immunisations and therefore the advice in the Netherlands requires monitoring vital signs of preterm infants during and 24 h after vaccine administration [2,29–32]. For this reason, infants born at GA <30 weeks are routinely monitored in case of immunisations and infants of older GA are hospitalised for initial immunisations based on medical indication [2].

In our study, 40% of all preterm infants received their first immunisations too late, a percentage that is higher than the 25% preterms found in an earlier Dutch study. For the term infants in the same study 82% received their first immunisation on time [16]. The difference may be partly explained by the more lenient definition of timeliness of the first immunisation used in that study with 63 days of postnatal age as upper age-limit to administer the first immunisations in our study and according to the Dutch Guidelines instead of the 70 days defined by Woestenberg et al. The delayed start of the primary series did not lead to further delays in the second and third immunisation in most cases, which is in contrast to findings by Scheepers et al., who explored immunisation timeliness in a large cohort of predominantly (96%) term infants [24]. This suggests different reasons drive the delay in term versus preterm infants.

Strengths of this study are the large size of the preterm cohort with 12 months follow-up, the detailed information on medical and socioeconomic risk factors and that all immunization dates were verified by research personnel. Furthermore, loss to follow-up was minimal. The comprehensive dataset allowed us to evaluate timeliness in detail and study important determinants of timely immunisation, such as GA, SES and duration of hospital stay.

A limitation of this study is that 48.1% of the included preterm children were born in a family with highest SES, which is more than in the general Dutch population. According to data from Statistics Netherlands, 30% of the adults in the Netherlands were highly educated in 2018 [33]. Possibly, the high SES in this study population is not fully representative of all families with preterm infants; this could have resulted in an overestimation of timeliness, since higher SES was associated with improved timeliness.

In conclusion, delayed start of immunisation occurs in 39.5% of all preterm infants in the Netherlands and differs for different GA groups, being lowest (37%) in infants <28 weeks GA. Lower SES

and prolonged hospital stay beyond 37 weeks GA are important determinants of timeliness. Subsequent immunisations are mostly provided according to schedule. Efforts to improve timeliness should focus most on counselling parents in lower SES.

Funding

This work was funded by the Dutch Ministry of Health, Welfare and Sport.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

Acknowledgments

The authors thank all participants and their parents/guardians who made this work possible by participating in this study. We would also like to thank all study nurses and clinical staff at the Centre for Infectious Disease Control, Bilthoven Netherlands and the participating hospitals.

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