Adverse events in premature infants born before 28+0 weeks of gestation after vaccination with Synflorix (PhiD-CV) and Infanrix hexa (DTPaHBV-IPV/Hib)

Version 2

Author: Kanar Shwan Anwar
Supervisor: Andreas Ohlin MD, PhD
Örebro university hospital, Sweden
Abstract

Introduction
Preterm infants have an immature immune system and are therefore recommended to be vaccinated at 2 months age. But studied have shown that preterm infants acquire cardiorespiratory side effects because of the vaccines.

Aim
The aim was to investigate the frequency of adverse events developed in infants, born before 28+0 weeks after being vaccinated with Infanrix hexa (DTPa-HBV-IPV/Hib) and Synflorix (PhiD-CV).

Material and method
All children born 2012-2014 before 28+0 weeks of gestation with mothers resident in Örebro county were enrolled. A total of 29 children were investigated. All the children’s medical charts were collected and read through to investigate the side effects 72 hours post vaccination.

Results
A total of 62.1 % of the infant acquired some kind of adverse event determined to be vaccine related. Desaturation was the most common side effect developed in 41.4 %, followed by fever 37.9 %, apnoea 27.6 %, fatigue 27.6 %, bradycardia 24.1 % and injection site pain a 3.4 %. Significance association was found between gestational age < 26 week or vaccinated when < 70 days old and increased incidence post vaccination fever. It was also observed that infants with no assisted ventilation or oxygen nasal prongs compared to infants using CPAP or respirator care had an increased incidence of apnoea and bradycardia, but decreased incidence of fever.

Conclusion
Observations were made that preterm infants do receive side effects due to the vaccines. But these results should be considered with caution because of the risk that the medical charts were wrongly interpreted.

Keywords: Preterm infant < 28 weeks, vaccination, adverse events
Abbreviations

CPAP - Continuous positive airway pressure
IgG/IgM/IgA - Immunoglobulin G/M/A
CD4/8 - Cluster of differentiation 4/8
LPS - Lipopolysaccharide
Th1/Th17 - T-helper cell 1/17
ELISA - Enzyme linked immunosorbent assay
OPA - Opsonophagocytic activity
PT - Pertussis toxoid
FHA - Filamentous haemagglutinin
PRN - Pertactin
HBs - Hepatitis B surface antigen
PRP - Polyribosylribitol phosphate
APGAR - Appearance, Pulse, Grimace, Activity, Respiration
CRP - C-reactive protein
Table of content
1. Introduction ................................................................................................................. 4
   1.1 Neonate immune system ......................................................................................... 4
   1.2 Synflorix (PhiD-CV) .............................................................................................. 5
      1.2.1 Product characteristics .................................................................................. 5
      1.2.2 Immunogenicity .............................................................................................. 5
      1.2.3 Adverse events ............................................................................................... 6
   1.3 Infanrix hexa (DTPa-HBV-IPV/Hib) ....................................................................... 6
      1.3.1 Product characteristics .................................................................................. 6
      1.3.2 Immunogenicity .............................................................................................. 6
      1.3.3 Adverse events ............................................................................................... 7
   1.4 Swedish vaccination program .................................................................................. 8
2. Aim ............................................................................................................................... 8
3. Material and method ..................................................................................................... 8
   3.1 Study sample .......................................................................................................... 8
   3.2 Data collection ........................................................................................................ 9
   3.3 Statistical analyses ................................................................................................ 10
   3.4 Ethics ...................................................................................................................... 10
4 Results .......................................................................................................................... 11
   4.1 Study population .................................................................................................... 11
   4.2 Patient characteristics ........................................................................................... 11
   4.3 Incidence of adverse events ................................................................................... 12
5. Discussion .................................................................................................................... 14
   5.1 Limitations ............................................................................................................. 16
6. Conclusion .................................................................................................................... 17
References ........................................................................................................................ 17
1. Introduction

1.1 Neonate immune system

The neonatal immune system, particularly those prematurely born, is thought to be undeveloped and inclined to invasive infections [1]. Preterm infants have low maternal IgG levels because during the pregnancy, the highest amount of antibody’s that cross the placenta from the mother to the foetus occur the last 4 weeks of the third trimester. These antibodies have a large role in protecting the infant against infectious diseases [1,2]. At birth infants are at a state of leucocytosis. These leucocytes decrease in number and the majority of the premature children are later neutropenic.

All neonates have more naive cells at birth. They show depressed polymorphonuclear leucocyte function and lower count activated neutrophils [3,4]. Infants have an inadequate myeloid progenitor and neutrophil storage pool, and the discharge and mobilisation of the neutrophils from the bone marrow is reduced. [1] These polymorphonuclear cells in preterm children have an impaired response to lipopolysaccharide (LPS), and when stimulated with LPS have a diminished production of neutrophilia extracellular traps. These extracellular traps are important to enclose pathogens [5]. They have also shown decreased chemotactic, adhesive and opsonic properties [4]. This diminishes the neutrophils defence against infections. Neutrophils in infants suffering from septicaemia and respiratory distress syndrome seem to have diminished mobility, chemotaxis and to have less oxidative activity [1]. Mononuclear cells have impaired cytokine response and monocyte response to antigens is impaired but this is not dependent on functional impairment of the monocytes phagocytosis capability [6]. Toll like receptor 4 is a vital LPS receptor and it is expressed to a lesser extent in preterm children’s leukocytes [7].

In the first week of life, the T helper cells start increasing in amount and stabilise at three month of age. The B cells reach their highest number between 1-6 weeks [8]. Preterm, compared to term infants have significantly lower T-cells, B-cells, T-helper cells and absolute lymphocyte count. Preterm children also have lower CD4/CD8 ratio [9]. The CD4+ T-helper cells are essential for the recognition of foreign antigens [10]. Neonates seem to have a more T-helper cell 2 and Th17 polarized immune system rather than pro-inflammatory Th1 response [11]. This is believed to be a defensive measure so that the child is not rejected from the mother, but as a consequence the infant has deficient viral detection [12].
Neonatal B-cells produce less antibodies IgG and IgA than adult B-cells. The neonate T-cells express less degree CD40 ligand compared to adults and more compared to preterm neonates. This leads to deficient T cell activated B cells and defect antibody class switch. This is negative for the B cell since the CD40 ligand is needed for production of IgA an IgG so that not only IgM is produced [12,13].

1.2 Synflorix (PhiD-CV)

1.2.1 Product characteristics
The 10-valent pneumococcal non typeable Haemophilus influenzae protein D-conjugated vaccine (PhiD-CV) also known as Synflorix is comprised of ten streptococcus pneumoniae specific polysaccharide serotypes. They are called 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. Eight of these serotypes (1, 4, 5, 6B, 7F, 9V, 14 and 23F) are conjugated to a protein D derived from non-typeable Haemophilus influenza. 18C is conjugated to tetanus toxoid carrier protein and 19F is conjugated to diphtheria toxoid carrier protein [14]. The serotypes 6A and 19A are cross-reactive [15].

1.2.2 Immunogenicity
One study used three parallel groups of infants, group 1 was infants with gestational age ≥ 27-< 31, group 2 (≥ 31 - < 37) and group 3 (< 37 weeks). They were all given three priming vaccine doses at 2, 4, and 6 months of age followed by a booster dose at 16-18 months [15]. To measure the concentrations of the pneumococcal serotype specific IgG a 22F- inhibition enzyme-linked immunosorbent assay (22F-ELISA) was used. Seroprotective antibody concentration is determined as 0.2µg/mL. This is equivalent with 0.35µg/mL with an ELISA without 22-inhibiton, which is the reference determined by the World Health Organization. Another way to measure immunogenicity of the vaccine is via opsonophagocytic activity (OPA) titer, with a cut of titer of ≥ 8 [15,16]. At least 92.7% of the infants in each group reached ≥ 0,2µg/ml in antibody concentrations one month after the three primary doses and 93.2% of the infants had OPA titers ≥8 for all serotypes. The exceptions were serotype 19F and 5 in group 1. In all groups, serotypes 1 and 6B had lower OPA titers. One month after the booster vaccination, 97.6% of the infants in each group had an antibody concentration of ≥ 0.2µg/ml for all the included pneumococcal serotypes. The antibody concentrations increased 5.7-24.3 fold after the after the booster dose [15].

The vaccine can be given in either a three dose priming plus one booster or two dose priming plus one booster. The immunogenicity of the two schedules has been investigated, and
concluded that there was a trend of lower immune response in the two priming and booster vaccination group than the 3+1 [16]. The serotypes 6B and 23F concentrations were lower than the other serotypes in general but even lower in the 2+1 group. Less infants reached the OPA cut off ≥8 when measuring serotype 1, 6B, 18C, 23F and 5. After the booster dose a significant increase in antibody concentrations were observed for all serotypes [16,17]. At 36-46 months old, those infants who received a 2 dose priming plus a booster dose, 83.7 % were still seropositive for all vaccine serotype and the cross-reactive 19A. Those who got 3+1, at least 96.5 % were seropositive against all vaccine antigens and 86.4% against 19A [17].

1.2.3 Adverse events
Irritability, is the most frequently reported general adverse event post primary and booster doses. The second most common adverse event after the primary vaccination is redness at the injection site and after the booster dose, pain at the injection site [17]. The incidence of redness and swelling as local solicited adverse event are higher in full term infants compared to preterm infants after both primary and booster doses. Symptoms can be scored on an intensity grading scale between 1 and 3. Redness and swelling at the injections site with grade 3 intensity, that is > 30mm in diameter, are reported in ≤ 5.3% after primary vaccine doses in both preterm and full term groups. Post booster, full term infants have higher incidence compared to preterm [15].

1.3 Infanrix hexa (DTPa-HBV-IPV/Hib)

1.3.1 Product characteristics
Infanrix hexa is a hexavalent diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliovirus and Haemophilus influenzae type b conjugated vaccine (DTPa-HBV-IPV/Hib). The vaccine contains diphtheria and tetanus toxoids. Three Bordatella pertussis antigens, Pertussis toxoid (PT), Filamentous haemagglutinin (FHA) and Pertactin (PRN). Three poliovirus subtypes (type 1 Mahoney strain, type 2 MEF-1 strain and type 3 Saukett strain). It also contains hepatitis B surface antigen (HBs) and Haemophilus type b polysaccharide (polyribosylribitol phosphate, PRP) conjugated to tetanus toxoid [18].

1.3.2 Immunogenicity
Three studies have all documented the hexavalent vaccine giving a good humoral immunity being safe and stimulating an immunologic memory [19-21]. After giving 3 priming doses the seroprotetive rate reached at least 95.7 % for all antigens. After the booster dose, 98.4 % had seropositive antibody levels for all vaccine antigens. After a 2 priming doses, the seropositive
antibody levels were at 83.4 % and 97.9 % after the booster against all vaccine components [22]. The booster vaccination given between 12-18 months is well tolerated and gives a strong increase in antibody titers for diphtheria, tetanus, HBs, PRP and the three polio viruses. This results in a 98.4-100% seroprotection rate [19,22]. For the three pertussis antigens 97.4 % of the infants responded to the booster dose.

Over 90% are seroprotected against all vaccine antigens between 3.5-4 years after administration of the booster vaccine [19]. Children 4-8 years old were seropositive in 91% of the cases against all three polio viruses and PRP. Seroprotection rate against diphtheria and tetanus were 64.7 %. Against the three pertussis antigens 25.4 % were protectively immunogenic against PT, 97.5 % FHA and 87.0 % against PRN. Between the ages 4-5 ≥ 85 % were protected against hepatitis B and ≥ 72 % when between 7-8 years old [22]. The anti-pertussis antibodies decrease in concentration with time [19].

Preterm infants have shown good immune response to the vaccine antigens [20]. After three priming doses given at 2, 4 and 6 months old, 98.7 % are seroprotected against diphtheria, tetanus and polio type 1 and 2. At least 90.9 % were seropositive for hepatitis B, PRP and polio type 3 and for the three pertussis antigens [22]. After a booster dose between 18-24 months of age, 98.4 % of the premature infants are immunologically protected against all vaccine antigens except for PT (96.8%) and Hepatitis B (88.7%). The antibody response to polio type 2 is incomplete when Infanrix Hexa is administered with Synflorix but it is thought to be clinically insignificant [22]. It has also been demonstrated that a combination vaccine with DTP and Hib give a lower antibody response to Hib. However, it is not believed to have a clinical importance [23,24].

1.3.3 Adverse events
The most common local adverse events following the vaccination is redness. Drowsiness is reported to be the most, and loss of appetite the least frequent systemic symptom [21]. In preterm infants the most frequently reported symptom is irritability [20]. A study showed that 4.3% of the adverse events were causally related to the vaccination. 2.6 % had serious adverse events, but the majority were not considered to be correlated to the vaccine. [21]. The majority of unsolicited adverse events reported occurred in infants with gestation age <28 weeks. These events were desaturation, bradycardia and apnea episodes [20]. It has been observed that several of the adverse events occurring in premature infants also occur in full term. Fever reactions in infants is more common if Infanrix Hexa is co-administered with a
protein conjugated pneumococcal vaccine for example Synflorix [22]. Studies have shown that most of the cardiorespiratory adverse events post vaccination are clinically mild to moderate and the infants returned to baseline 48-72 hours later [25,26].

1.4 Swedish vaccination program
Swedish children born after 2002 are vaccinated against diphtheria, tetanus, polio, pertussis and haemophilus influenzae type b at 3, 5 and 12 months. Then when 5-6 years old they are vaccinated again against diphtheria, tetanus, pertussis and polio and when 14-16 years old they receive a last vaccine against only tetanus, diphtheria and pertussis. At 3, 5 and 12 months they are also vaccinated against streptococcus pneumonia [27,28]. Vaccine against hepatitis B are given three times either with the other vaccines, or according to another scheme [28].

At Örebro University hospital, it is recommended that infants born earlier than 32+0 weeks, or have a birth weight < 1500 grams should be vaccinated at 2-month age. If necessary they can be vaccinated at 50 days old, otherwise they should have reached the equivalent of 34 weeks of gestation. This recommendation exists because preterm infants have higher risk of infection compared to full term. [Apendix 1].

2. Aim

The aim of this study was to investigate what kind of adverse events premature infants born before 28+0 weeks of gestation received when administered with the vaccines Infanrix Hexa and Synflorix at two month of age. This is of importance to know because of the recommendation that very premature infants should be vaccinated at 2 months old even if they are prematurely born. Furthermore, investigated was how many of them were vaccinated and what vaccine they received.

3. Material and method

3.1 Study sample
The study population is comprised of all the children born before 28-week of gestation 2012-2014, whose mothers are resident in Örebro county. Children who died before they could be vaccinated were excluded from the study.
Figure 1. Gathering the study population. 9780 were born with mothers resident in Örebro 2012-2014 [29]

3.2 Data collection
An excel file was made where we documented all the observations. The data analysed about the infants were divided into four major groups. Group one was information about the child before vaccination such as way of birth, age, birth weight, length and head circumference. Further, we looked for if they had received antibiotics and counted the total number of days they were administered antibiotics before vaccination. If steroids had been administered, the number of days without steroids prior to the vaccination was counted.

Group two was information about the mother. We looked for her age when giving birth and if she had gotten any steroids during the pregnancy. Group three was facts about the child during the day of vaccination that is age, what kind of assisted ventilation they used and what type of vaccine they received.
The last group were the documentation of the adverse events during the 72 hours post vaccination compared to 72 hours prior to the vaccination. Increased oxygen need with at least 5 percentage points during a minimum of 12 hours, an increase in frequency of apnoea (≥20%), bradycardia (≥20%), any desaturations and fever (≥37.5°C) were analysed. Noticeable injection site pain, affected eating habits, experienced fatigue or acquired diagnosed neurological seizures were all documented. Further, we investigated if they needed their current assisted ventilation more than usual or if they had to change to something else because of the vaccine. Other side effects and possible explanations were documented. The definition of apnoea used by the department is cessation of respiration ≥ 20 seconds with need of stimulation to recover. Bradycardia is defined as decreased heart rate to under 100 beats per minute.

At the end a final evaluation was made for each patient answering one question. Has this patient gotten any side effects that can be determined as vaccine related, considering everything investigated? If the answer was yes to the question, they got the final evaluation as having had a side effect because of the two vaccines.

Some of the information, especially the patient characteristics before vaccination and some information about the mother was received form the Swedish neonatal quality register. Everything else was collected from the patient medical charts at Örebro University hospital and documented in the excel file.

### 3.3 Statistical analyses

Microsoft Excel 2016 was used to calculate the frequencies of adverse events and to calculate mean, minimum and maximum values. Pearson chi square test and Fishers exact test were used to calculating all statistics. If any of the expected sample groups were less than 5, the probability value calculated by Fishers exact test was considered. To calculate the Pearson chi square and Fishers exact test the programme SPSS (IBM SPSS statistics version 23) was used. The probability value considered to be statistically significant was ≤ 0.05.

### 3.4 Ethics

This study was conducted at Örebro university hospital as quality management and therefore no ethical approval was required. No information was given to the patients about the study and therefore no consent was collected. Authority to read the medical charts was signed by the head of department. All patient data were de-identified and no individual data is published. But it is important to recognize that people’s personal charts were read and because
there are so few infants that are born at such an early gestational age, it is not impossible for participants conducting the study to recognize the children. And therefore all information was used with absolute confidentiality.

4 Results

4.1 Study population
A total of 36 children were born before 28-weeks of gestation. Of the 36 infants, 7 died between 0-42 days of age which meant that they had not been vaccinated and were therefore excluded from the study. Two children were discharged before 72 hours had passed post vaccination, but they were still included in the study. Giving a total study population of 29 new-borns.

4.2 Patient characteristics
Of the 29 children, 15 were female and 14 males. Eighteen of the children were delivered via caesarean section and 11 were born via vaginal birth (see table 1). The infants varied in gestational age between 23+6 and 27+5 weeks with the mean gestational age being 26+1 (see table 2). Their birth weights varied between 465-1175 grams with mean weight at 826.3 grams. The mean age when vaccinated were 69 days within a range of 59-89 days. All infants were given antibiotics and 52% were administered with postnatal steroids at some time before they were vaccinated. 26 out of 29 children (90%) had mothers that were administered with steroids during the pregnancy.

Table 1. The frequency between the number of male and female infants regarding their way of birth

<table>
<thead>
<tr>
<th>Caesarean section (n)</th>
<th>Vaginal birth (n)</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>86 % (12)</td>
<td>14 % (2)</td>
</tr>
<tr>
<td>Female</td>
<td>40 % (6)</td>
<td>60 % (9)</td>
</tr>
</tbody>
</table>

At the time of immunization 24 infants out of 29 (83%) still had some sort of assisted ventilation. Five (20.8%) had continuous positive airway pressure (CPAP), 2 (8.3%) were still intubated, 6 (25%) were alternating between CPAP and supplemental oxygen via nasal prongs and 11 (45.8%) were only using oxygen nasal prongs.
Table 2. Patient characteristics before vaccination

*Total days between last dose with steroids and day of vaccination. The mean value is calculated on the 52 % (15 out of 29) of the infants that were administered with steroids at any time before vaccination.

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Max</th>
<th>Min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total gestation time in days</strong></td>
<td>183 (± 6.7) (26+1)</td>
<td>194 (27+5)</td>
<td>167 (23+6)</td>
</tr>
<tr>
<td>(Weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Birth weight</strong></td>
<td>826 (± 188)</td>
<td>1175</td>
<td>465</td>
</tr>
<tr>
<td>(gram)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Length (cm)</strong></td>
<td>33.2 (± 2.4)</td>
<td>37</td>
<td>29</td>
</tr>
<tr>
<td><strong>Head circumference (cm)</strong></td>
<td>23.8 (± 1.5)</td>
<td>27</td>
<td>20.5</td>
</tr>
<tr>
<td><strong>Mothers age (years)</strong></td>
<td>30 (± 4)</td>
<td>38</td>
<td>23</td>
</tr>
<tr>
<td><strong>Total days with Antibiotics</strong></td>
<td>17.7 (± 11)</td>
<td>42</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total days without steroids</strong></td>
<td>19.4 (± 13,5)</td>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td><strong>Age when vaccinated (days)</strong></td>
<td>69 (± 7.5)</td>
<td>89</td>
<td>59</td>
</tr>
</tbody>
</table>

4.3 Incidence of adverse events

The vaccination coverage was 100% and all infants were vaccinated with Synflorix (0.5 ml) and Infanrix Hexa (0.5 ml). 62.1 % of the infants was evaluated as having had an adverse event because of the vaccine. The most common adverse event was desaturations which occurred in 41.4 % of the infants (see figure 2). The other adverse events in a decreasing scale were fever (37.9%), apnoea (27.6%), fatigue (27.6%), bradycardia (24.1%) and pain at the injection site (3.4%). Four infants (13.8%) got elevated CRP (C-reactive protein). Other adverse events are presented in figure 2.

As previously mentioned, every infant was evaluated in the end to determine if they had any adverse events because of the vaccines. Calculations were made comparing several pre immunization factor with this end evaluation. No significant association was found between gestational age (born before 26 weeks), birth weight (under 800 grams), mothers age over 30 years, antibiotics administration ≥14 days, having any assisted ventilation at all or not, < 70
days when vaccinated, or if the infant had received steroids and having any adverse events at all as end evaluation.

**Figure 2. Frequency of adverse events post vaccination**

Apnoea, bradycardia, fever and desaturation were evaluated separately. Infants with no assisted ventilation, or only in need of oxygen nasal prongs (group 1), were compared to infants who still to some degree were in need of CPAP or were still intubated (group 2) at the time of the vaccination. It is statistically significant that the infants first mentioned (group 1) had an increased incidence of apnoea ($p=0.014$ Fishers exact test) and bradycardia ($p=0.035$ Fishers exact test) after the vaccine. Group 1 had significantly lower incidence of fever post vaccination compared to group 2 ($p=0.011$ Pearson chi-square).

Infants born before 26+0 weeks had significantly higher incidence of fever post immunization ($p=0.039$ Pearson chi-square). Fever is significantly decreased in children < 70 days of age when vaccinated ($p=0.003$ Fishers exact test). Aside from already mentioned findings, no additional significant association was found between gestational age (born before 26), birth weight ($\leq$ 800 grams), postnatal age <70, way of birth, antibiotic administration $\geq$14 days or receiving any postnatal steroids and developing increased number apnoea, bradycardia, fever or desaturations.
5. Discussion

In this study we investigated retrospectively the side effect frequency in children < 28 weeks, when administrated with the two vaccines Synflorix and Infanrix hexa. 62.1 % had some kind of side effect judged to be vaccine related. The most frequent side effect was desaturation with 41.4 % followed by fever 37.9%, apnoea 27.6%, fatigue 27.6% and bradycardia 24.1%.

Previous studies have documented infants with prematurity associated cardiorespiratory symptoms, for example apnea, bradycardia and desaturation, having higher incidence of those events post immunization [26,30]. 63 % of infants with persistent prematurity associated symptoms had an increase in adverse events after being vaccinated [25,26]. In this study, 62.1 % developed or had an increase of already existing symptoms. Prior studies have shown that following vaccination with either Infanrix (DTPa-IPV+Hib) or Infanrix Hexa (DTPa-HBV-IPV/Hib), 13-39 percent of preterm infants had an increased incidence of apnoea [26,31]. In infants without apnoeic episodes when vaccinated, 11% relapsed after the immunization. Children with immaturity-associated bradycardia or desaturation episodes before the vaccine had a significant rise after the immunization, in 32 % and 52 % respectively. Infants bradycardia or desaturation episodes before the vaccination relapsed in 14% and 17 % respectively [26]. In this study, no consideration was made to differentiate between having or not having prematurity associated cardiorespiratory symptoms, and comparing it to post vaccination symptoms. However, it was presented that apnoea occurred in 27.6 %, bradycardia 24.1 % and desaturation in 41.4% of all infants. Some of these percentages documented in our study do not differ considerably form the prior studies.

To our knowledge, previous studies have not observed any significant association between an increase in cardiorespiratory events when correlated with gestational age, birth weight or postnatal age (when vaccinated) [25,32]. And this study could not show any correlations between these factors and cardiorespiratory side effects either. Considering these findings, maybe it is yet beneficial to vaccinate these infants at 2 months. Conversely, in this study some observations were made regarding fever. With 37.9 % of the infants developing fever post vaccination, it was the second most common adverse event. Infants born before 26+0 weeks had an increased risk of developing fever after the vaccine $p=0.039$.

It has been detected that infants that are vaccinated, when they are younger than 70 days, have a higher risk of developing adverse events [32]. In this study we saw that infants younger than
70 days when vaccinated had a significantly decreased incidence of post vaccination fever \( p=0.003 \). But no significant association between the end evaluation of having any side effects at all, and being younger than 70 days, was found. This could perhaps be because infants of different ages are prone to different side effects. But observed in this study was that infants needing CPAP at any time or who were intubated (previously mentioned group 2) had significantly increased incidence of fever. This would therefore contradict the last statement, because it could be arguments that infants with need of CPAP or respirator care at the time of vaccination have more immature lungs and are therefore most likely younger. Hence these two findings would contradict each other.

It is known that when the body is exposed to pathogens (LPS), the different immune cells recognize these with the help of toll like receptors. When that has occurred the cells start producing several cytokines such as prostaglandin E2, tumour necrosis factor, interleukin 1 and 6. These together, with several other components, elicit a fever reaction [33]. Conversely, we are also aware that preterm infants have an immature immune system [1]. Could this possibly be an explanation for the finding that <70 old infants have significantly lower incidence fever? Because if the infant is older, their immune system is capable of eliciting the reactions necessary to rise the body temperature. Considering our findings, additional studies are necessary to investigate the subject further.

In this study, depending on what type of assisted ventilation the infants had at the time of vaccination, they were divided into 2 groups. Group 1 were the infants without any assisted ventilation and those using only oxygen nasal prongs. Group 2 were all infants that to some degree still needed CPAP or were intubated. The children in group 1 had significantly more post vaccination apnea and bradycardia, \( p=0.014 \) and \( p=0.035 \) respectively. It could be argued that this is a sign of the infants still having premature lungs and therefore developing more apnea. But it can likewise be debated that infants with either CPAP or respirator care have even further immature lungs, and why did they not acquire more apnea? Possibly, this could be because CPAP and respirator care helps the infant’s premature respiratory system [34,35] and therefore we could not observe an increase in apnea in these children. And indeed there are two infants in group two that are intubated. Even if these significant associations are interesting findings, it is important to remain critical.

When collecting the data observations were made that some of the infants in this study were given paracetamol when they developed fever. Studies have shown that prophylactic
paracetamol administration gives a lower antibody response to some of the vaccine antigens in Synflorix [17,36]. It is however unclear what this has for clinical significance [17].

To our knowledge, no similar studies have been conducted, investigating only children < 28 weeks. Therefore, this issue is an important field in medicine to be investigated. However, in this current study, many calculations were made comparing numerous different factors with the adverse events documented. Because of this, it is important to recognize that some of our findings might just be coincidence even though the probability values were lower than 0.05.

5.1 Limitations
The information considering the 72 hours post vaccination was gathered from patient medical charts retrospectively. In there the nurses documented the infant’s daily activity and situation. They documented if they have had an apnea, bradycardia, fever and much more. But it is difficult to know exactly if what they have written is what actually happened medically according to the hospital’s qualification criteria, or if it just was the nurse’s interpretation of the situation. Some nurses were very detailed in their descriptions and were careful with not using for example the word “apnea” if it was not a qualified apnea. Many were not so detailed and accurate in their descriptions, which made it difficult to know if one situation in one child was the same as in another. One of the most difficult things to evaluate was if the infant after the vaccination needed more oxygen or not. Because a lot of the time the infant had an apnea and the nurse automatically increased the oxygen percentage, or the infant had a desaturation and the nurse did the same. This made it difficult to know when it was actually needed and for how long the oxygen was increased. This is a large weakness in this study. It is mostly based on how detailed the nurses write what has happened in the medical charts and how those notes are interpreted. Further the results in this study is based on a small population sample and therefore should be considered with caution.

Many other studies have looked at redness or swelling at the injection site, which often has been documented as quite a frequent side effect. And they have also graded the side effects to evaluate how serious the adverse events are [15,19,21,24,25]. This is something that was not done in this study. But might be something to consider to receive more exact results even if redness might not be considered of high clinical importance for the infant.
6. Conclusion
In this study, observations were made that 62.1% of the infants had a side effect related to the vaccine. The most common side effect was desaturation followed by fever, apnea, fatigue and bradycardia. Therefore, we can conclude that preterm infants do acquire some type of vaccine related adverse events. But perhaps it is still benefited to vaccinate the infants to protect them from infection. However, studies with more precise criteria, larger study samples and better ways to collect the data are needed for more reliable results. Especially if it is still recommended that these infant are vaccinated at 2 months.

References

1. Maria Björkqvist. Coagulas - negative staphylococci septicaemia in newborns Aspects on host-bacterial interactions with special regard to neutrophil and endothelial responseFaculty Of Health Science Linköping University; 2004 (11-26).


