Adverse events induced by first immunization in extremely premature infants

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Abstract

Introduction: Infants born prematurely have immature immune system, making them vulnerable to vaccine-preventable diseases. For this reason it is important they receive their immunization in time. No factors except from being unstable are an argument to postpone it and the dosing should be the same as for full term infants. However, vaccination to premature infants not always stimulate enough antibody titers and this low titers may be more declined over time. Adverse events, especially cardiorespiratory, are reported from several studies to be regularly experienced in premature infants. It is uncertain wherever there are any distinguishable risk factors, such as birth weight or gestational age, to predict adverse events.

Aim: The primary aim was to study the incidence rate of adverse events within 72 hours after first immunization, in infants born before 28 weeks´ gestation. The secondary aim was to study what type of event and how many events that developed.

Materials and method: 27 extremely premature infants, born before 28 weeks´ gestation, from Jönköping, were subject to the study. Sequence of adverse events were considered vaccine-related if they were absent before vaccination and present within 72 hours after or if their frequency increased within 72 hours postimmunization. The study was made by a retrospective, population-based, cohort study.

Results: All patients in the study population received the vaccines. 33% of all included infants had at least one adverse events after immunization and seven of these had more than one adverse event. The most common events were increased oxygen requirements, desaturations, fatigue and body pain/dissatisfaction. No correlation to gestational age, birth weight or age at immunization were observed.

Conclusion: Adverse events, often more than one, are prevalent in extremely premature infants. This results in an advice to monitor the infant after immunization, although continue to vaccinate at two months of chronological age. The benefits of having the vaccine has to overweight the risk of experience AE.

Keywords: premature infant, vaccination, adverse events, premature infant´s vaccination, antibody titers
**Abbreviations**

EPI- extremely premature infant  
PI- premature infant  
AE- adverse event  
FTI- full term infant  
Ig- immunoglobulin  
AB- apnea and bradycardia  
GA- gestational age  
BW- birth weight  
Hib- Haemophilus influenza type b
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1. Introduction
Clinicians suspect it to be prevalent with adverse events (AE’s) after immunization with Infanrix hexa and Prevenar in extremely premature infants (EPI’s), which can be troublesome. For instance, there were as much as 38% of 45 premature infants (PI’s) who had vaccine-induced AE’s such as apneas, bradycardias and desaturation [1] and fever developed in 33-34% in very PI’s [2,3]. Given that AE can cause trouble in EPI’s, this study aim to examine the incidence rate of AE in EPI’s.

1.1 The premature infant
Infants are premature when born before gestational week 37, which is mainly because disease of the mother, such as high blood pressure or placenta insufficiency [4]. When born preterm the infants can be small for gestational age and have intrauterine growth restriction [5].

The immature infant is in several ways undeveloped with many immature organs, which increases their mortality rate. For example, the lungs are immature with surfactant deficiency, which makes breathing difficult. The lower gestational age (GA) the more undeveloped are the lungs [4]. This immaturity of the lung is what is seen in respiratory distress syndrome [6]. Additionally, ductus arteriosus are shut later than normal or remain open, leading to low systemic blood pressure and increase in pulmonary blood flow with lung edema [4]. When born more than 2 months premature, the digestive and absorptive functions are almost always inadequate [4,6]. Also the liver is immature, which results in bleeding tendency, hypoproteinemic edema and anemia [6].

1.2 Premature infant’s immune system
Due to immature immune system and depressed production of all immunoglobulins (Ig’s) [6], PI’s are immunocompromised at birth and more vulnerable to vaccine-preventable diseases [1]. The low production of Ig’s are because PI’s have low monitored B and T lymphocytes [7,8], which act in a less effective way and express immature cell surface receptors [8]. These receptors develops most prominent during the third trimester [9], resulting in less specific and weaker interactions with antigens and as earlier mentioned, decreased antibody synthesis in PI’s [8,10]. PI’s also have less efficient switch from low affinity Ig to higher affinity Ig, because immature T-B cell interactions [10]. However, the immune system develops gradually during the first 2 years, indeed the later the vaccine is administered the more effect it has [9].
To succeed with the immunization two problems must be overcome. The first major problem is fewer and malfunctioning antigen-presenting cells, which leads to polarization toward Th2. Overcoming this polarization is best done through stimulation of toll like receptors, thus promoting Th1 polarization. The second problem is passive immunization from mother’s antibodies [11], the more antibodies the higher is the impact on the infant [9]. Maternal antibodies affect the infant via binding antigen epitopes, thus giving infant’s B cells no opportunity to access these epitopes. This is however not a problem in extremely premature infants because the transplacentally transferred antibody reaches equilibrium during the 33rd week of gestation [7]. Overcoming passive immunization is best done through adjuvants [11] and the only adjuvant that has been approved in the neonates vaccines is a form of aluminum hydroxide [12], which is ineffective in neonates because it does not promote Th1 immunity [11].

1.3 Premature infant’s vaccination
PI’s are often given the vaccines delayed, because medical complications and practitioner concerns for the premature infants fragility and ability to get immunized [13,14]. Even though, the PI’s should receive the childhood recommended vaccines in the same doses and at the same recommended chronological age as full term infants (FTI’s) [13]. Regarding factors to postpone the first immunization, low GA, low birthweight (BW) or low calendar age giving vaccine are no such factors. In fact, the only factor to postpone the immunization is when the infants is clinically unstable [7,9] and in these situations the advice is to do the vaccination in hospital setting [7]. Another recommendation is to not give live virus vaccines to PI’s [15].

The infants born before gestational week 28 are especially immunologic immature and have defects in responding to vaccination [8]. In the fact of that, the infants born in Sweden with BW under 1500g or born before 32 weeks’ gestation, are advised to have an extra dose of vaccination at two months of chronological age. After the first extra dose the remaining three doses are administered at 3, 5 and 12 months of chronological age [16].

1.4 Adverse events
The most prevalent occurring AE’s in infants after receiving Prevenar and Infanrix hexa are, fever, pain at injection site, food intolerance and irritability [17,18]. In EPI’s born before 28 weeks’ gestation apnea can be present in 2-3 days after vaccination [18].

AE’s in PI’s prevalently involve the cardiorespiratory system, which is observed in 51% of the infants with very low BW [19]. Previous studies have shown that the risk for
cardiorespiratory events are higher if PI’s are vaccinated before day 70 [1] and the more extremely immature the infant is, with lower postmenstrual age and weight [8,20]. For instance, infants born at gestational week 23 or 24 had higher risk of intubation and all extremely low birth weight (<1000g) infants had increased respiratory support and intubation after routine immunization [21]. Therefore it is vital to evaluate the cardiorespiratory status and medical history to reduce the risk of AE after administering vaccine [7].

Several studies have examined the apnea and bradycardia (AB) frequency after immunization and the results are ambiguous. For example, PI’s (GA <37 weeks) receiving vaccine compared to the PI’s not receiving it, were no more likely to experience AB [22] and only 17 of 98 PI’s, with GA at 24-31 weeks, developed AB [2]. Moreover, 87% (mean GA 28 weeks) tolerated their first vaccination well, and no one of the 13% infants with AB needed CPAP or intubation [23]. In contrast, of 850 PI’s, born in 23-35 gestational week, it was shown 0-47% got worsening or new onset of AB after their vaccination, although most of them were mild symptomology [8]. Similarly, 47% of 78 infants (mean GA 28 weeks) had an adverse reaction. Of these, 15% had apnea and 21% had bradycardia, which were mostly benign and with no influence on the clinical course [24]. When comparing the infants who got AB and the ones without there were indistinguishable risk factors [23].

The results about different risk factors to predict AE are diverse. It is observed that AE’s are more prevalent in infants with severe clinical condition, such as having premature associated apnea, bradycardia [9,10,24] or bronchopulmonary dysplasia at the time of immunization [19]. Moreover, apnea was more frequent in babies with lower GA and BW [19,25]. In contrast, GA, BW or age at immunization cannot predict AE incidence in PI’s [1,2,9,24] nor can postnatal weight at vaccination [21].

When studying the components in the different vaccine, AE after a combined vaccination was the same for PI’s and FTI’s, which suggest that combined vaccination does not result in more AE’s [21,26]. In terms of adding acellular or whole cell pertussis component to the vaccine, AB frequently appeared when using the latter [20]. In contrast other results show incorporating Pa instead of Pw component did not prevent postvaccination apnea in PI’s [23].

1.5 Antibody titers

Critical for protection against infections are production of antigen-specific-antibodies [11] and vaccination to PI’s do not always stimulate adequate antibody titers [8] For instance, although PI’s had seroprotection after the third administration, the geometric mean antibody
titers were lower for tetanus, diphtheria, polio [20] and pertussis in PI´s than in FTI´s [8,10]. In particular, it was shown that the antibody concentration was lower with a BW of less than 1500g compare to other heavier infants [27] and the observed lower antibody titers became more pronounced lower over time [8,28]. By way of contrast, another report shows tetanus, diphtheria and pertussis antigens immunogenicity were equal in FTI´s and PI´s [10].

The Haemophilus influenza type b (Hib) vaccine efficacy depends on the infant´s overall health and the choice of carrier protein conjugated to the antigen. Even though bound to a carrier protein, it may have deficiencies resulting in immunization in PI´s [10]. For example, if GA is less than 27 weeks, the response to Hib might be weak and the vaccine then generates poor immunogenicity [8]. Although lower titers of anti-Hib antibodies are observed, that is not associated with impaired protection against the disease [20].
2. Objective

Adverse events in preterm infants had been examined several times. Although many of these did investigate a specific adverse reaction or the study population were not extremely preterm born. Therefore the objective of this study was to investigate if there were any adverse events related to vaccination in extremely premature infants, when retrospectively scrutinizing their medical records.

2.1 Aim

The primary aim was to study the incidence rate of adverse events within 72 hours after first immunization, in infants born before 28 weeks’ gestation. The secondary aim was to study what type of event and how many events that developed.
3. Materials and method

3.1 Study population
This study is a retrospective, population-based, cohort study, where medical records from EPI’s have been examined. Infants from Jönköping’s county, born before 28 weeks’ gestation formed the subjects of the study. Infants born before gestational week 27+0 are in the beginning taken care of in University Hospital in Linköping and then transferred to Ryhov Hospital in Jönköping. We studied data covered infants born from 1/1, 2012 through 31/12, 2014. In total 29 infants were identified. 27 were included and were subjects in the study. The two excluded died before vaccination. Medical records were reviewed retrospectively in April 2016. Patients were identified from SNQ, which is a nationally cooperation established to improve care of neonates. All infants treated in neonatal care unit are registered in SNQ in conjunction with labour or within 28 days after [29].

3.2 Vaccination
Included infants recevied Infanrix hexa 0,5 ml, and Prevenar 13 0,5 ml. Infanrix is a vaccine for diphtheria, tetanus, pertussis, hepatitis B, polio and Haemophilus type B. Prevenar is a vaccine for pneumococcus [30]. It was after the first vaccination dose events related to vaccination were studied. The first dose is recommended to be administered at two months of chronological age, but we studied all patients even though not receiving it in that exact time. Adverse events within 72 hours after immunization were reported as an event.

3.3 Study protocol
38 different parameters from the medical records were collected by the investigator (appendix). Parameters noted preimmunization were for example gender, gestational age, birthweight and birth length. The medical history before and at vaccination were also studied. Postvaccination, different reactions such as bradycardia were analysed. The reactions were compared pre- and postimmunization and an assessment if adverse events were present or absent were done. Bradycardia was defined as a heart rate of less than 80/min, apnea as more than 10 seconds without breathing and fever when temperature was over 37,5 degrees Celsius. All the reactions were assessed as adverse events if they were recorded as AE’s in the medical charts or if the investigator noticed a new reaction or increased frequency of a reaction postvaccination. Sequence of adverse events were considered vaccine-related if they were
absent before vaccination and present within 72 hours after or if their frequency increased within 72 hours postimmunization.

3.4 Statistics
The statistical analysis was performed in SPSS (Statistical Package for the Social Science) using Fisher’s exact test, which is recommended when there is less than 5 patients in the columns. For subgroup analysis the patients were divided into different groups, one with and without adverse event and the other according to birth weight, gestational age or age at immunization. These groups were compared to each other to see if there were any statistical difference. P< 0.05 was considered statistical significant.

3.5 Ethical consideration
Information was collected retrospectively from medical charts at Ryhov Hospital Jönköping in Småland, Sweden. The records contained data classified as confidential, therefore ethical aspect had to be taken into consideration. All included patients were identified with an unidentifiable number and the records scrutinized were handled with care. The study was performed with quality assurance approval in Jönköping, but with no ethical declaration approval.
4. Results

During 2012-2014, 11710 babies were born at Ryhov hospital [31-33] and of these, 29 EPI´s were identified. 2 of those died before vaccination, therefore the study population consisted of 27 EPI´s (12 males and 15 females). The infant´s median gestational age at birth was 26+3 weeks, with median birthweight of 835 grams and median length of 34 centimeters. All 27 included in the study received the vaccine, as illustrated in figure 1.

![Flowchart](chart.png)

*Figure 1: Flowchart of all infants born 2012-2014, included study population and frequency of adverse events. N stands for number of patients.*
In table 1 the characteristics and details of the infants are summarized. Of the 27 infants 11 weighted under 800 gram and 20 were born via cesarean section. The majority had CPAP or oxygen requirements and 50% had mechanical ventilation, maintained for at least one week before vaccination. Additionally all but three had received antibiotics before vaccination, however only 6 had culture confirmed sepsis. 82% had patent ductus arteriosus and 44% of the infants received systemically steroids postnatally.

*Table 1: Basic characteristics and clinical conditions of the infants. Records from labor to first immunization. Regarding “<1 week and >1 week”, these explain how long time the infants had the three different ventilation supports.*

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>Boy</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Girl</td>
<td>15</td>
</tr>
<tr>
<td><strong>Delivery</strong></td>
<td>Vaginal</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Cesarean section</td>
<td>20</td>
</tr>
<tr>
<td><strong>Gestational, weeks+days</strong></td>
<td>Median (min.-max.)</td>
<td>26+3 (23+2-27+5)</td>
</tr>
<tr>
<td><strong>Birth length (cm)</strong></td>
<td>Median (min.-max.)</td>
<td>34 (28-39)</td>
</tr>
<tr>
<td><strong>Birth weight (grams)</strong></td>
<td>Median (min.-max.)</td>
<td>835 (385-1174)</td>
</tr>
<tr>
<td><strong>Head circumference (cm)</strong></td>
<td>20-24</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>24+</td>
<td>10</td>
</tr>
<tr>
<td><strong>Apgar 1</strong></td>
<td>0-5</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>6-10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>No data</td>
<td>1</td>
</tr>
<tr>
<td><strong>Apgar 5</strong></td>
<td>0-5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>6-10</td>
<td>22</td>
</tr>
<tr>
<td><strong>Apgar 10</strong></td>
<td>0-5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>6-10</td>
<td>26</td>
</tr>
<tr>
<td><strong>Mechanical ventilation (duration)</strong></td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>&lt;1 week</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>&gt;1 week</td>
<td>13</td>
</tr>
<tr>
<td><strong>CPAP (duration)</strong></td>
<td>&lt;1 week</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;1 week</td>
<td>26</td>
</tr>
<tr>
<td><strong>Oxygen (duration)</strong></td>
<td>&gt;1 week</td>
<td>27</td>
</tr>
<tr>
<td><strong>Antibiotics (days)</strong></td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>1-20</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>20+</td>
<td>6</td>
</tr>
<tr>
<td><strong>Sepsis</strong></td>
<td>No</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td><strong>Bacteria</strong></td>
<td>CoNS</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus species</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Enterococcus species</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>S. Aureus</td>
<td>1</td>
</tr>
<tr>
<td><strong>Patent ductus arteriosus</strong></td>
<td>No</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>22</td>
</tr>
<tr>
<td><strong>Postnatal steroid treatment</strong></td>
<td>No</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>12</td>
</tr>
</tbody>
</table>
Most of the patients (n=16) received the vaccine at the age of 50-70 days and the majority (n=23) had some kind of ventilation support at that time. The median postnatal age at first immunization was 67 days. The status at vaccination are given in table 2.

Table 2: Patient’s status at vaccination.

<table>
<thead>
<tr>
<th>Age at vaccination (days)</th>
<th>Median</th>
<th>67 (55-87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilation support</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Mechanical vent.</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>CPAP</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Oxygen</td>
<td>12</td>
</tr>
</tbody>
</table>

9 of 27 (33%) EPI’s experienced at least one adverse event in this study, which is clarified in table 3. The most common occurring adverse events were increased oxygen requirements, desaturations, fatigue and bodypain/dissatisfaction. However no neurologic seizures or food intolerance had been recorded.

Table 3: EPI’s adverse events experienced within 72 hours postimmunization and assessment. The reaction was assessed to be an AE if it was recorded as an AE in the medical charts or if the investigator noticed a new reaction or increased frequency of a reaction postvaccination.

| Increased oxygen requirement | 4 |
| Desaturation                 | 4 |
| Fever                       | 2 |
| Apnea                       | 3 |
| Pain at injection site      | 2 |
| Bradycardia                 | 1 |
| Increased ventilation support | Oxygen | 1 |
|                             | CPAP   | 1 |
| Food intolerance            | 0 |
| Fatigue                     | 5 |
| Neurologic seizure          | 0 |
| Pain/dissatisfaction        | 4 |
| Assessment of adverse event | Yes | 9 |
|                             | No    | 18 |

Table four clarifies the frequency of having several AE’s. Seven of the nine infants had more than one AE. There were four patients having desaturations and increased oxygen requirements simultaneously. Two of them also had elevated ventilation support.
Table 4: Frequency having 1-5 adverse events.

<table>
<thead>
<tr>
<th>Number of adverse event</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

4.1 Subgroup analysis

For subgroup analysis the infants were divided into different subgroups. The first subgroup analysis was made by dividing the infants into two groups, one group EPI’s born earlier than 26 weeks’ gestation and the other after. There were nine EPI’s born before gestational week 26 and of these, two experienced adverse event. Of the 18 EPI’s born after week 26, seven had AE. The difference of having AE in the earlier and later born group is considered not to be statistically significant (p=0.67) when using fishers exact test.

The second subgroup was made according to birthweight, one group with birthweight under 800 grams and the other above. There were 11 EPI’s born with a weight under 800 grams, of these five had adverse reactions. Of the 16 EPI’s with BW over 800 grams, four had AE. The difference from the light and heavy group is not considered to be statistically significant (p=0.41) when using fishers exact test.

The third subgroup was divided according to their age at immunization, one group receiving it before 70 days and the other after. 11 received vaccination later than 70 days of age and two of them had AE. As a consequence seven of the 16 infants receiving it before 70 days of chronological age had AE. This difference is not considered to be statistically significant (p=0.23) when using fishers exact test.
5. Discussion

The aim of this present study was to examine how frequent vaccine induced AE’s occurred in EPI’s after the first vaccination. The results indicate that immunization frequently induces AE’s in EPI’s. The most frequent existing AE’s were increased oxygen requirements, desaturations, body pain/dissatisfaction and fatigue. Having several events present simultaneously was also common.

The rate of experienced AE’s in this study was 33%, which is almost exactly what an earlier report shows, however, the infants in that report were older [1]. Many of the 27 infants included experienced AE that involved the cardiorespiratory system, which is in line with previous studies [19,21]. Furthermore, previous reports have evaluated AB but the results are ambiguous. For example, Carbone T. et al [22] suggest there is no increased risk for PI’s to experience AB but in contrast, Schulzke S et al. [23] state that 13% had an increased frequency of AB. Apnea was seen in three patients (11%) in the present study, which is similar to Pfister R.E et al.’s evaluation and bradycardia was experienced in only one patient (3,7%) which does not coincide with Pfister R.E et al.’s results [24]. However, Pfister et al.’s study and the other reports mentioned above included a larger and more mature study population. Considering fever, only two (7,5%) of the 27 patients had it, which is a lower frequency compare to other studies and Fass [2,3,17].

In fact, it can be difficult to draw any definitive conclusions about the incidence of AE’s since there are few medical chart notations on these fragile infants, which makes it difficult to distinguish AE’s induced by vaccination from background instability and other variables.

In this study birth weight and gestational age were examined to see if there were any correlations to vaccine-induced AE’s. The previous results about this varies, some demonstrate that GA and BW do not affect AE frequency [1,2,9,24]. However, others state the opposite [8,19,20,25]. The anticipated finding was that the lightweight and earlier born PI’s would have more adverse events since the more preterm born child the more immature is the PI [7,9]. However, the subgroup analysis in this study showed no significant difference when comparing different BW/GA and AE incidence. Therefore it seems not to be a higher frequency of AE in the infants with very low BW/GA compared to the infants with extremely low BW/GA. It may be difficult to make predictions concerning BW or GA since some infants have the same weight even though they are born in different gestational weeks, which
means they will have various degrees of maturity. In these cases the maturity degree have more impact on the risk of experiencing AE than the weight. It is however difficult to compare these results with previous studies because the ones mentioned above are made with more mature infants.

In this study the correlation of AE incidence and age at immunization was also examined. Infants receiving the vaccine before 70 days were anticipated to have more AE according to Sen,S et al. [1]. In contrast, DeMeo S.D et al. [21] showed that the age at immunization could not predict the AE incidence postvaccination. As in the earlier mentioned analyses, this subgroup analysis showed no correlation between AE and age at immunization. To summarize, these three subgroup analyses showed no distinguishable risk factors regarding BW, GA and age at immunization, which is in line with Schulzke S.’s report [23].

Even though there were no statically significant differences found when comparing the three subgroups mentioned above, the results could have been different if the sample size would have been larger. In the future it would be interesting to examine if there are any risk factors. Indeed, it is possible this study can generate other new studies and if the results from these indicate AE to be related to some factors, there is a potential to be able to better monitor and improve special care in infants with these risk factors, so the incidence rate of AE’s decline. Alternatively future studies may show some special care to be unnecessary.

Immunization delays are common and a possible reason according to Saari T.N et al. [13] is that physicians are unlikely to prescribe the vaccine to an unstable infant. However, if the delay is prolonged there is a potential risk of getting vaccine-preventable diseases. In the present study the delay was observed in 11 infants but mostly only about 10 days, and therefore the influence on the infant is probably minimal [16].

There were as many as 33% that experienced AE’s. Preferably these AE’s should be reported to the medical product agency, but there are doubts about if they are. If more AE’s would be reported to the medical product agency there will be a better opportunity to show how frequent a specific AE and AE’s in general are in these EPI’s in Sweden, which can lead to better monitoring and perhaps a decline in AE incidences.

The primary limitation in this report is the recording of AE’s. To start with, the assessment and the recording of the reactions postvaccination can vary from one nurse to another. What some nurses interpret to be an AE others do not, which results in different recordings of the reactions. The nurses may also be more likely to record AE occurring in close proximity to
vaccination administration, resulting in more records after than before. This bias could have been reduced if pre-/postimmunization episodes would have been blinded. Furthermore, there is likely a greater underreporting of mild AE’s in general, because attention is mostly on the more severe AE’s, which are probably more consistently documented. Another limitation in this area is the investigator’s analysis of the medical records. The reactions were assessed as AE’s when they were recorded as that in the medical charts and when the reactions had an increased frequency or when new events occurred after vaccination. However, this vague definition made it possible to assess the reactions in several ways. This potential bias could have been reduced if having two independent investigators or if the definitions of AE’s would have been more precise. Because of the retrospective nature of this study it is difficult to standardize and control observations and monitoring. For example, as mentioned above, if the definition of AE is vague, it is possible to do various assessments based on the monitoring of the infant. Therefore in the future, it would be helpful to have a standardized form of the reactions after vaccination, which could result in more identical assessments and recordings of the reactions.

Another limitation is the small sample size, which can cause rare AE’s to be undetected. Moreover the small study population makes it difficult to draw any definitive conclusions about the risk factors predisposing the EPI’s to vaccine induced AE’s. Hypothetically it could have been possible to compare all the basic characteristics with the incidence rate of AE’s, but because the study population was not large there would still be difficulties in finding any correlations. For example, this study did not investigate the risk of being clinically unstable at immunization and the experienced AE’s. The incidence rate is, however, anticipated to be higher in infants with a history of medical complications [9,10,21,24]. If the sample size would have been larger it would have been possible to evaluate if being unstable results in higher frequency of AE’s.

The strength of this study is that it gives an initial overview of the incidence rate of AE’s in extremely premature infants which is a relatively unexplored area. Another strength is that it is population based. Thus, the results might make it possible to generalize them to a bigger population and calculate prevalence rates, which can be compared with future studies. However, the present population represents an extremely vulnerable group, indicated by their low BW and GA, and therefore the results cannot be generalized to PI’s in general.
In this study the two vaccines Infanrix and Prevenar were administered simultaneously, which made it difficult to determine which one of the two vaccines and which component resulted in AE´s. For example it is suggested that the type of pertussis component added to the vaccine could affect the outcome and that live-attenuated virus vaccines are potentially more prone to lead to reactions in the infant [20]. However, no more AE´s were reported after combination vaccines [21,26]. The examination of which component might lead to development of AE was not the aim of this study.

6. Conclusion

Our study was consistent with previous studies evaluating AE after immunization, reporting AE to be present in many cases. All infants included received Infanrix hexa and Prevenar routine immunization and adverse events were experienced in many extremely premature infants and more than one reaction at a time was frequently observed. The most prevalent events were increased oxygen requirements, desaturations, fatigue and bodypain/dissatisfaction. Nor low GA, low BW or earlier immunization were found to be risk factors for experiencing AE. Immunizations were sometimes delayed about 10 days when the infant was clinically unstable. The recommendation is to continue to administer vaccine at two months of chronological age and to provide cardiorespiratory monitoring after administration. A decision has to be made about each PI concerning the benefits from immunization and the risk of experience AE. The benefits from immunization need to outweigh the risk of AE. It is difficult to draw any definitive conclusions from this study because of the limited study population. However, future larger studies can make it possible to discover how to lower the incidence rate of AE´s.

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9. Appendix

The 38 parameters studied were:

Before vaccination

- Personal identity number
- Gender
- Delivery
- Gestational age
- Birth weight
- Birth length
- Head circumference
- APGAR at 1, 5 and 10 minutes
- Present or absence of mechanical ventilation, CPAP and oxygen
- Duration of antibiotics
- Sepsis (yes/no) and the bacteria causing it
- Patent ductus arteriosus (yes/no)
- Have had postnatal steroids (yes/no) and the last administering day
- Mothers age and if she have had prenatal steroids

At vaccination

- Infants age
- Present or absent ventilation support and what type (mechanical ventilation/CPAP/oxygen)
- Dose and type of vaccine that was administered

After vaccination (present, yes or no)

- Increased oxygen requirement
- Desaturation
- Fever
- Apnea
- Pain at injection site
- Bradycardia
- Increased ventilation support and what type (mechanical ventilation/CPAP/oxygen)
- Food intolerance
- Fatigue
- Neurologic seizure
- Assessment if AE were present or absent