University of Cape Town, Health Sciences Faculty

# A single-centre *Preterm infant Retrospective Analysis of post 6-week Immunisation Side-Effects*, 'PRAISE' study, in a busy neonatal unit in the Western Cape, South Africa between 2016-2018

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**Abbreviations:**

| | |
|---|---|
| U5MR | Under-five year Mortality Rate |
| VPD | Vaccine Preventable Disease |
| EPT | Extreme Preterm |
| VPT | Very Preterm |
| LPT | Late preterm |
| ELBW | Extremely Low Birth Weight |
| VLBW | Very Low Birth Weight |
| LBW | Low Birth Weight |
| GA | Gestational Age |
| cGA | corrected Gestational Age |
| AEFI | Adverse Event Following Immunisation |
| WHO | World Health Organisation |
| LMIC | Low- and-Middle Income Countries |
| MMH | Mowbray Maternity Hospital |
| NICU | Neonatal Intensive Care |
| MOU | Midwife Obstetric Unit |
| EPI | Expanded Programme on Immunisations |
| HREC | Human Research Ethics Committee |
| UCT | University of Cape Town |
| HoD | Head of Department |
| HAI | Hospital Acquired Infection |
| BC | Blood Culture |
| FBC | Full Blood Count |
| CRP | C-reactive Protein |
| IPPV | Intermittent Positive Pressure Ventilation |
| CPAP | Continuous Positive Airway Pressure |
| HFNC | High Flow Nasal Cannula |
| NPO2 | Nasal Prong Oxygen |

**Definitions**

| | |
|---|---|
| Extremely Preterm Infant | GA <28 weeks at birth |
| Very Preterm Infant | GA <32 weeks at birth |
| Moderately Preterm | GA between 32-33 weeks+6 days |
| Late Preterm | GA between 34 weeks and 36 weeks+6 days |
| Preterm infant | A baby born less than 37 completed weeks. |
| Extremely Low Birth Weight (ELBW) | <1000g |
| Very Low Birth Weight (VLBW) | ≥1000-1499g |
| Low Birth Weight (LBW) | ≥1500-2499g |

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**Publication ready manuscript:**

The following manuscript has been prepared for submission to The South African Medical Journal (SAMJ). The journal's aims and scope, as well as author guidelines, are provided in Appendix A.

A single-centre *Preterm infant Retrospective Analysis of post 6-week Immunisation Side-Effects*, 'PRAISE' study, in a busy neonatal unit in the Western Cape, South Africa between 2016-2018

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**Abstract**

Background: Vaccine-Preventable Diseases (VPDs) are a leading cause of the high Under-five Mortality Rate (U5MR). Preterm infants are inherently at higher risk of mortality from VPDs. Studies irrefutably show the benefit of vaccinating preterm infants according to their chronological age with the benefit of timely vaccination outweighing unjustified delays. However, later studies have shown an increased risk of adverse events (AEs) following immunisation (AEFI) in preterm infants. This risk has not been uniformly accepted as statistically significant, but the multiple reports have led to subsequent proposed 48–72-hour cardio-respiratory monitoring recommendations which have not been uniformly adopted and may not be feasible in Low-and-Middle Income Countries (LMICs).

Objectives: The main objective of this study is to identify the prevalence of major AEs following 6-week immunisation of preterm infants admitted to a busy neonatal unit in Cape Town over a two-year period. AEFI will be scrutinized to ascertain the timing, clinical severity and possible contributing factors. This study aims to identify any consistent variables or a subset of higher-risk preterm infants to inform a safe and practical in-hospital preterm vaccination and monitoring protocol.

Methods: A retrospective audit was conducted on 260 eligible, in-patient, preterm infants receiving the 6-week vaccination as per the South African Expanded Programme on Immunisation (EPI) schedule from 01 March 2016 -31 March 2018 at a busy secondary-level maternity referral hospital, Mowbray Maternity Hospital (MMH).

Results: Two hundred and sixty (260) participants were included in the study, the median gestational age (GA) was 29 weeks, median birth weight 1 078 g and the median age at immunisation 44 days. Thirty-eight (38) out of the 260 participants (14.6%) experienced an AEFI with a median birth GA 28 weeks and median birth weight 988 g. Twenty-nine (29) out of 38 were deemed immunisation-related, since no other cause could be identified, with a prevalence of 11.15%. Majority (89.4%) of AEFI occurred within 24 hours. GA was inversely proportional to the risk of an AEFI. Respiratory support was needed by 73.7% and 97% were screened and treated for sepsis.

Conclusion: Established benefit exists in vaccinating preterm infants according to chronological age. However, due cognisance should be paid to the early preterm infant's higher risk of AEFI, 11.15% in our study. Our study supports a clear unit-individualised preterm immunisation protocol with a minimum 24 hours of cardio-respiratory monitoring post vaccination, especially in the very preterm infants <32 weeks GA.

## Introduction

The global burden of prematurity is steadily increasing and according to a systematic review, was estimated to be ~ 10.6% in 2014 with more than 81% of these occurring in Asia and sub-Saharan Africa.[1] In South Africa, the true national burden of preterm birth is unknown.[2] Despite notable advances in neonatal intensive care leading to increased survival rates amongst the extreme preterm (EPT) population group, many of these children still die or need hospitalisation during the first year of life, with a significant number still due to vaccine preventable diseases (VPD).[3]

Vaccination remains one of the most successful and cost-effective public health intervention to date.[4] However, a statistically significant proportion of the under-five year mortality (U5MR) is still attributed to VPD.[5] Preterm infants are inherently at higher risk of morbidity and mortality caused by VPD, inversely proportional to both gestational age (GA) and birth weight.[3, 6] The timely administration of immunisations, especially among the EPT and very preterm (VPT) infants remain a clinical challenge subject to individual bias, despite the recommendations to vaccinate preterm infants according to their chronological age and following the same schedule as that of full term infants.[3, 7] Initially, many argued inferior vaccine efficacy and immunogenicity in the preterm population as reason to delay.[3, 8] Fortunately, evidence showed that postnatal immune maturation in preterm infants occur with continued environmental exposure to antigen at a rate comparable to full term infants.[7] Several studies have established good vaccine efficacy and immunogenicity, but recent studies continue to highlight the variability in preterm immunisation practice.[9]

Vaccine-safety and fear of AEFI is a consistent reason for unjustified vaccine delays among EPT and VPT infants.[7] Whilst timely vaccination is strongly advocated for in this vulnerable population, the existing higher risk of AEFI cannot be ignored. Multiple studies since 1990 illustrate an increased risk and frequency of significant AEFI in the preterm population worldwide. Many of these AE may be short-lived and of no consequence if acted upon swiftly. Due to these reports, consensus groups now recommend 48-72-hour in-patient cardio-respiratory monitoring for post birth vaccination of all preterm infants.[10-12] This may not be feasible in a LMIC due to resource constraints. Formal recommendations are needed in LMICs to standardise the level of care in the neonatal setting.

Mowbray Maternity Hospital (MMH) only introduced chronological preterm immunisations from mid-2014. Anecdotally, one ex-preterm infant experienced apnoea's soon after discharge and another whilst un-monitored in the kangaroo mother care (KMC) unit, within 72 hours of their 6-week immunisations. These were thought to be unrelated to immunisation at the time and were unfortunately not extensively investigated but did lead to the creation of the individual MMH nursery preterm vaccination guideline in 2015. This guideline stipulates that "any preterm infant with ongoing cardiorespiratory events, including apnoea and bradycardia or oxygen desaturation should have the 6 or 10 or 14 week immunisations deferred until there are no such episodes for 48hours AND then observed with pulse oximetry for 48 hours after the immunisation is given".[13] This guideline does not provide directive for monitoring of the stable preterm with no such events prior to immunisation. The practise at MMH since late 2015 however, has been to admit all preterm infants to the nursery for cardio-respiratory monitoring irrespective of their prior clinical status for a minimum of 24 hours and not to discharge until clinically stable for 48 hours post immunisation. This is reflected in the current protocol.(Appendix D) This study followed to ascertain whether this

practice was effective and safe and what monitoring guidelines are feasible given constant bed constraints.

**Objectives:**

The primary objective is to establish the true prevalence of significant adverse events (AE) post, in-patient, preterm 6-week immunisations.

Our secondary objective aims to identify patient factors that place them at an increased risk for an AEFI to guide a feasible and safe monitoring protocol for a busy LMIC neonatal unit.

An adverse event following immunisation (AEFI) is defined by WHO as any unpredictable negative medical occurrence post vaccine administration. [14]The said AEFI may or may not be related to the use of the vaccine. [14]

WHO further categorises AEFI into two: serious and non-serious. An AEFI is considered serious if it is life-threatening and requires hospitalisation, prolongs existing hospitalisation or if the outcome is death.[15]An AEFI is non-serious when a reaction occurs within a few hours of administration with short resolution and posing little or no damage [15].Severe AEFI reflect the intensity of a specific event (mild, moderate or severe). In this study, only serious AEFI leading to prolonged hospitalisation of our in-hospital preterm population were included.

There are cause-specific definitions of AEFI. E.g. AEFI related to the inherent properties of the vaccine itself or related to the product quality, an error-related reaction or coincidental, where the vaccine or any part related to the vaccine itself, is not the cause for the adverse event.Prematurity itself places the infant at inherent risk for features consistent with AEFI , e.g. apnoea, desaturation and bradycardia.

**Methods:**

Study design
This was a retrospective observational study done over a 2-year period from 01 March 2016 to 31 March 2018.

Study setting
MMH is a secondary-level maternity referral hospital with around 11 000 deliveries per year. The hospital comprises of a 73-bed neonatal unit which offers all levels of neonatal care, including a 7-bed tertiary-level Neonatal Intensive Care Unit (NICU). MMH is also the main referral centre for six midwife obstetric units (MOU's) responsible for 11-12 000 deliveries per year, one district level hospital as well as a step-down centre for stable preterm infants from the tertiary, Groote Schuur Hospital.
MMH is therefore the primary referral centre for approximately 22 000 of the annual ~34 000 Metro-West deliveries, extrapolated from the Perinatal problem identification programme (PPIP) data for 2016-2018. MMH is thus a fair representative of the bulk of the preterm population in the Metro-West region in the Western Cape.

Study population
All MMH Neonatal unit in-patient preterm infants (<37 completed weeks GA) who received their 6-week vaccination as per the South African Expanded Programme on Immunisation (EPI) schedule between 01 March 2016 and 31 March 2018.

Data Collection
Data was collected from the MMH Neonatal unit nursing vaccination register and cross referenced with the MMH pharmacy vaccination database. From these registers, a total of 320 medical folders were obtained from on-site medical records, of which 260 patients were eligible and included in this study. The 260 eligible participants were all in- patient preterm infants receiving their 6-week immunisations during the 2-year study period. The study excluded term infants, participants receiving 10-week immunisations and medical folders not attainable from MMH records, e.g. folders sent to another institution. Clinical information needed for the study was obtained from the medical folders and participants were allocated individual study numbers to maintain anonymity. The desired data was entered into a predesigned Excel spreadsheet further secured by user login and password.

The National Health Laboratory Service results viewer, TrakCare, was used to review biological markers of sepsis such as culture of bodily fluids, Full Blood Count (FBC) with differential count and C-Reactive Protein (CRP). The study used a CRP >20 mg/L in addition to other mentioned biological markers and a suggestive clinical picture in keeping with sepsis, to identify participants with culture-negative probable sepsis, therefore excluding them from the true AEFI group.
A CRP value of >20 mg/L was used after a careful review of the available literature. This was done in an attempt not to ascribe slightly raised CRP values solely to sepsis. Studies have shown increased CRP levels within 48 hours post immunisation with multiple vaccines given simultaneously. A prospective observational study in 2007 by Pourcyrous et al, involving 239 NICU preterm infants at ≥ 2 months of age (mean GA 28 weeks) showed that infants who received multiple vaccines were almost 16 times more likely to have abnormal CRP values (>16mg/L) at 12 hours post vaccination.[16] This was in accordance with a small study by Balkundi et al in 1994 that showed median CRP levels of <4 mg/L pre-immunisation vs 10.4 mg/L at 24 hours and 18 mg/L 48 hours post DTP and Hib vaccinations.[17]

Data Statistical Analysis
Data was entered into Stata Release statistical software package for statistical analysis by an independent statistician. The study looked at the prevalence of serious AEFI post 6-week preterm immunisation, excluding all sepsis cases. We analysed the participant baseline characteristics and clinical variables for any significant association with AEFIs.

Categorical data was reported as proportions and derived using the Chi Square or Fishers exact test. Continuous data was reported as median (interquartile range (IQR) and p-values derived using the Mann-Whitney U-test. P-values of <=0.05 was accepted as statistically significant. Note, a p-value equal to 0.05 was included to accommodate for the small sample size of participants with adverse events in our study. This relaxes the conditions for a type 1 error.

We further described the prevalence of AEFI in the different WHO GA categories of preterm infants. The AEFI type, timing of occurrence and the intervention needed post event was also reviewed in the study.

The study attempts to illustrate the pick-up rate of serious AEFI using a 24 hour monitoring protocol.

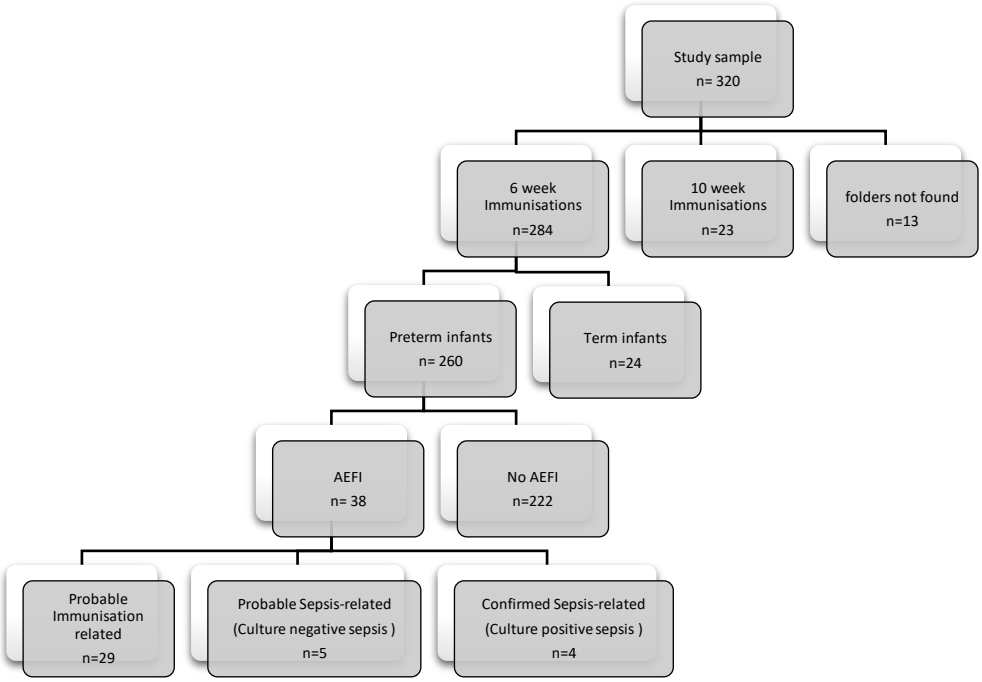
## Ethical considerations

This study entailed a retrospective folder review and informed consent was not obtained from parents of study participants. All personal identifiers were removed and all data anonymised. Ethics approval was obtained from the Human Research Ethics Committee (HREC), ref. no. 369/22, of the Faculty of Health Sciences, at the University of Cape Town (UCT). Furthermore, permission for clinical folder reviews were granted by the MMH Research Committee as well as the Head of Department (HoD) of the Neonatal Unit.

## Results

A total of 320 infants were vaccinated during the 2-year study period. Thirty-six (36) infants were excluded from the study of which 13 were due to folders not found and 23 who had received 10-week immunisations. Of the 284 who received 6-week immunisations, 24 were term infants and were excluded. A total of 260 preterm infants received 6-week immunisations and were included in the study. (Figure 1)

Figure 1: Flow diagram of study population: Inclusion, Exclusion and AEFI occurrence flowchart:




Thirty-eight (14.6%) experienced an AEFI. Of these, 29 AEFI were deemed immunisation-related as no other cause could be identified. This is a prevalence of 11.15%. Nine cases were not deemed immunisation-related, four of these cases had culture-positive sepsis and five cases had culture-negative sepsis.

Two culture-positive sepsis participants had late-onset Group B Streptococcal septicaemia, one participant had an extended β-Lactamase producing Klebsiela Pneumoniae on urine and one participant had a Streptococcus Viridans on blood culture.
Culture-negative but probable sepsis (Figure 1) referred to five participants, where a consensus decision was reached by two independent medical doctors after careful review of the medical and nursing notes regarding the clinical status of the participant as well as additional supportive biological markers.

Clinical baseline characteristics of all eligible participants were compared for the group with AEFI and the group without AEFI. (Table 1)

Table 1: Baseline characteristics of participants presenting for immunisation at 6 weeks.

| Characteristic | Total n=260 | Adverse event n=38 | No adverse event n=222 | p-value |
|---|---|---|---|---|
| Birth GA (weeks), median (IQR) | 29 (28-31) | 28 (28-30) | 29 (28-31) | 0.03 |
| Corrected gestational age at time of immunisation (cGA) (weeks), median (IQR) | 36 (35-38) | 35 (34-38) | 36 (35-38) | 0.07 |
| BW (g), median (IQR) | 1078 (910-1253) | 988 (860-1140) | 1100 (930-1280) | 0.01 |
| Age at immunisation (days), median (IQR) | 44 (42-47) | 45 (42-48) | 44 (42-47) | 0.43 |
| Weight (grams), median (IQR) at immunisation | 1700 (1485-1865) | 1610 (1395-1760) | 1713 (1500-1883) | 0.05 |
| Clinical variables: | | | | |
| Still receiving Caffeine at time of immunisation | 140 (53.9%) | 25 (65.8%) | 115 (51.8%) | 0.11 |
| Diagnosis of Bronchopulmonary dysplasia | 12 (4.6%) | 3 (7.9%) | 9 (4.1%) | 0.39 |
| Oxygen/ flow dependence, not BPD | 9 (3.5%) | 3 (7.9%) | 6 (2.7%) | 0.13 |
| Previous apnoea >7days prior | 63 (24.2%) | 12 (31.6%) | 51 (23.0%) | 0.25 |
| Apnoea within 7 days (>72hrs) prior to immunisation* | 4 (1.5%) | 1 (2.6%) | 3 (1.4%) | 0.47 |
| History of late onset sepsis, >7days prior to immunisation [#] | 105 (40.4%) | 18 (47.4%) | 87 (39.2%) | 0.34 |

Categorical data reported as proportions and derived using Chi square or Fishers exact
Continuous data reported as median (Interquartile range – IQR) and p-values derived using Mann-Whitney U-test and a p-value of =< 0.05 was accepted as being statistically significant. Note that a p value= 0.05 was included to cater for the small sample size of participants with adverse events in the study. This relaxes the conditions for a type 1 error.
*According to unit protocol during the study period, no infant was immunised if an apnoea occurred within the previous 72hours.
[#] According to unit protocol during the study period, no infant was immunised if sepsis within 7 days of immunisation age.

In Table 2 below, the birth GA was subdivided into the World Health Organisation (WHO) preterm categories and a comparative analysis made between those with AEFI vs no AEFI. The table further reflects an inverse trend in the proportion of reported AE's (21.4%, 14.5% and 9.4%) with increasing GA. However, the overall difference between the GA categories and AEFI does not reach statistical significance: chi-square p-value of 0.26.

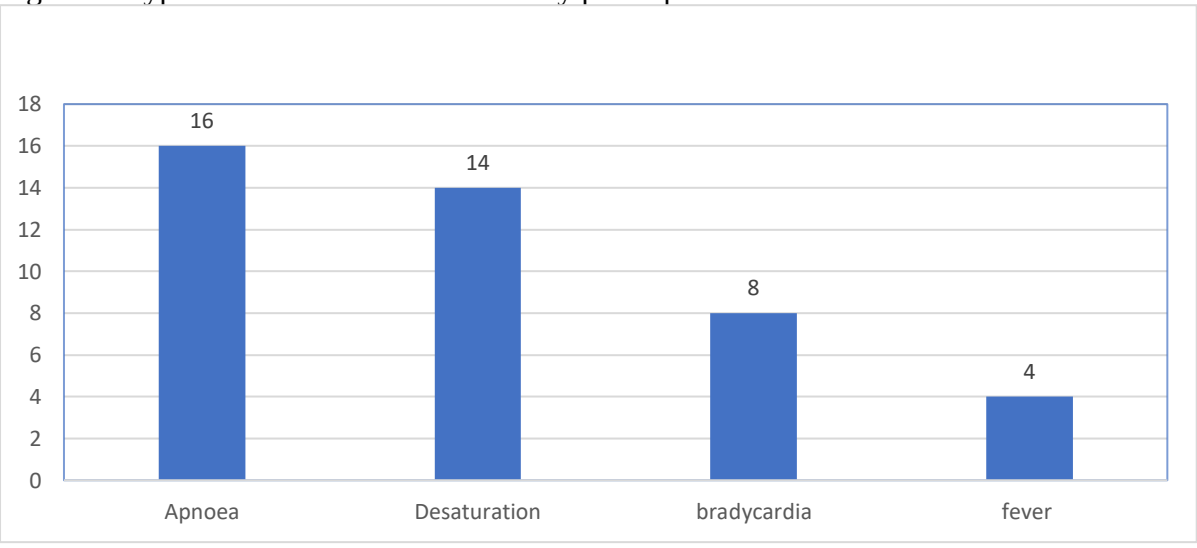
Table 2: Prevalence of AE in the different preterm GA groups

| Gestational Age at birth, number (n) | Adverse event | No adverse event | p-value |
|---|---|---|---|
| <28 weeks (extreme preterm), n=42 | 9 (21.4%) | 33 (78.6%) | p<0.001 |
| 28-31$^{+6}$ weeks (very preterm), n=165 | 24 (14.5%) | 141 (85.5%) | p<0.001 |
| 32-36$^{+6}$ weeks (moderate to late preterm), n=53 | 5 (9.4%) | 48 (90.1%) | P<0.001 |

p-values were derived using Z-test for proportions and a p-value<0.05 was accepted as being statistically significant

The type of AEFI recorded was reviewed independently and consensus reached by two medical doctors and defined on the basis of the clinical description in the medical and nursing notes. An apnoea was defined by cessation of breathing for 20 seconds or longer or a shorter period of cessation if associated with a bradycardia or cyanosis. Desaturation was defined as preductal saturation <88% not due to movement or artefact and persisting long enough for nursing staff to alert the attending doctor. Bradycardia was defined by a resting heart rate (HR) <80bpm and a fever as any temperature >37,5 degree Celsius.

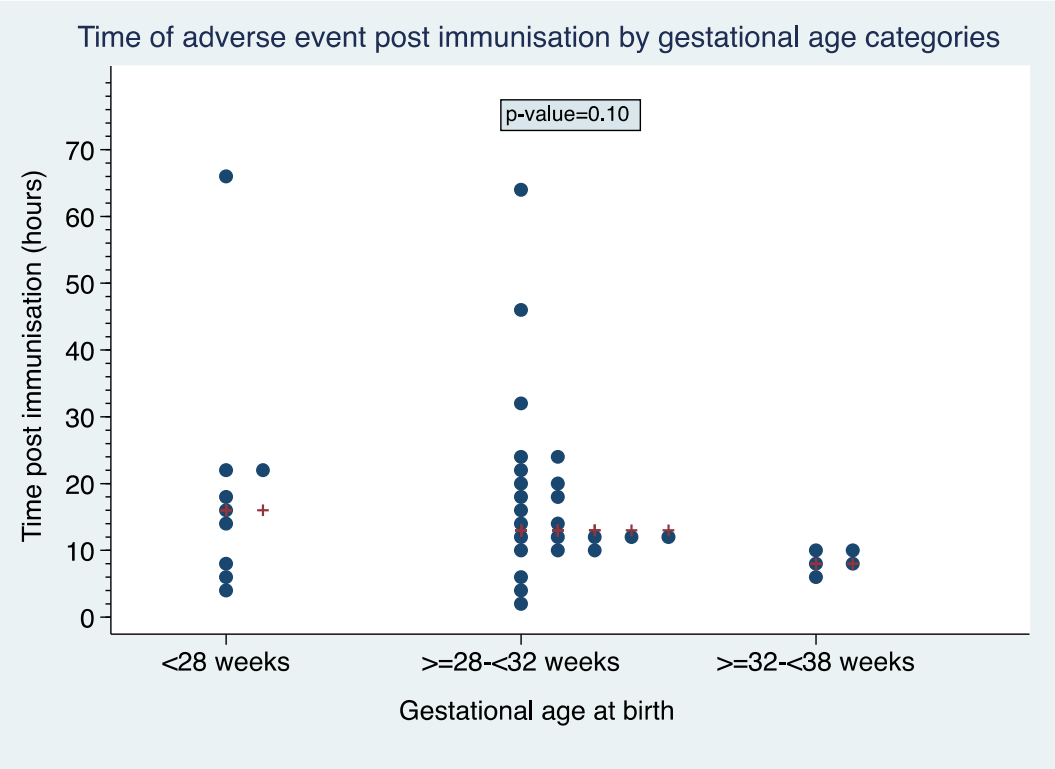
Figure 2: Type and number of AEFI in study participants



The timing of the AEFI showed that 34 (89.4%) occurred within the first 24 hours and 4 (10,6%) after 24 hours following immunisation. The median time for an AEFI was 12.5 hours post vaccine administration (Figure 3). The 4 participants with AEFI after 24 hours were all very preterm infants between 26-28 weeks GA at birth with one being a case with culture-positive sepsis.

Our calculated number needed to treat (NNT) for 24-hour monitoring of all VPT infants (<32 weeks): NNT = 1\ [(29/33) -(0/207)] = 1.14 = 2. NNT is calculated on the assumption that the exposed group are those who ultimately developed an AEFI (n=38).

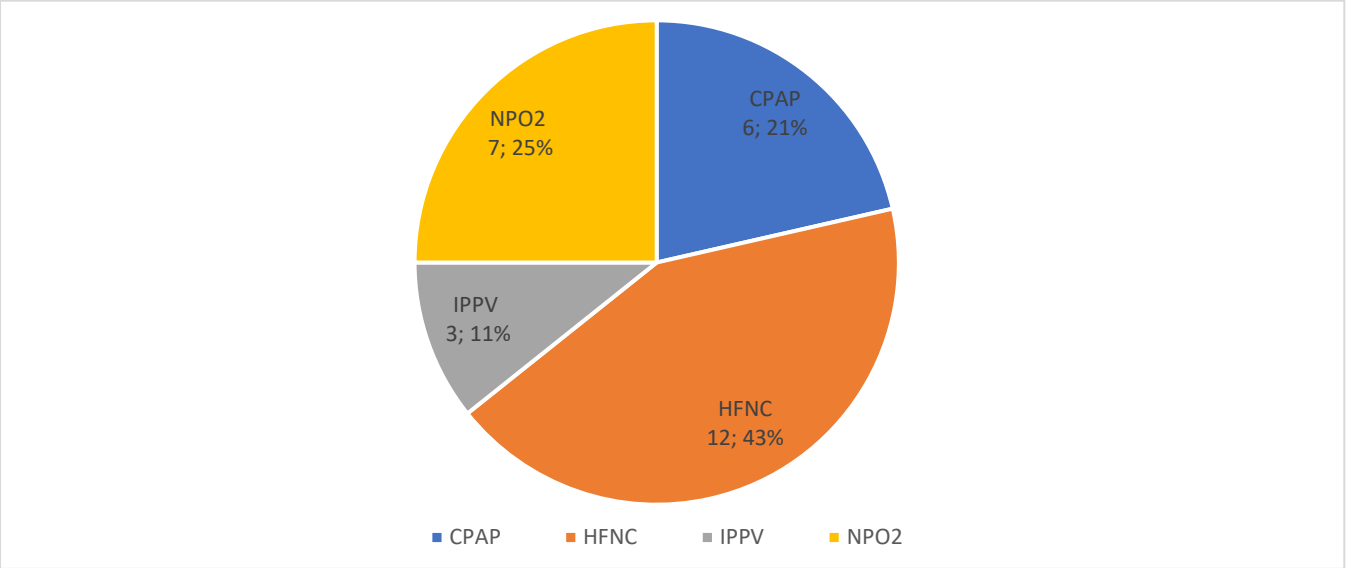
Figure 3: Time of AE post 6-week immunisation in the different GA categories




Further review revealed that 15 participants were discharged home just prior to completing 24 hours observation, 8 under 48 hours and 4 under 72 hours following their 6-week immunisation. The local Western Cape hospital database, Clinicom, confirmed no readmission or death of these participants within 72-hours post their 6-week immunisation.

The management interventions needed post AEFI are shown in table 3 below, in which 28 (73.7%) participants with an AEFI needed respiratory support (Figure 4).

Figure 4: Type of respiratory support needed for AE




Thirty-seven (97.4%) participants had a septic screen and was started on antibiotics. Only one participant was not screened for sepsis as the attending clinician opted for close monitoring only. This was a preterm at 32 weeks with a cGA of 38 weeks and a weight of 1865g, known with previous recurrent apnoea's, who had a very brief desaturation 8 hours post immunisation. One participant had a low haemoglobin (6.3g/dL) and required a blood transfusion, this participant also being one of the culture-positive cases.

Table 3: Management Interventions for AEFI:

| Post Adverse event interventions | Total (n=38) | Adverse event linked to immunisation (n=29) | Adverse event not linked with immunisation. (n=9) | p-value |
|---|---|---|---|---|
| Respiratory support | 28 (73.7%) | 20 (69.0%) | 8 (88.9%) | 0.40 |
| Type of respiratory support | | | | |
| IPPV | 3/28 (10.7%) | 2/20 (10.0%) | 1/8 (12.5%) | |
| CPAP | 6/28 (21.4%) | 3/20 (15.0%) | 3/8 (37.5%) | |
| HFNC | 12/28 (42.9%) | 8/20 (40.0%) | 4/8 (50.0%) | 0.20 |
| $NPO_2$ | 7/28 (25.0%) | 7/20 (35.0%) | 0 | |
| Septic screen with antibiotic cover[$] | 37 (97.4%) | 28 (96.6%) [$] | 9 (100%) | 1.00 |
| Blood transfusion[¥] | 1 (2.6%) | 0 | 1 (11.1%) | 0.07 |

[$]As per unit protocol, a septic screen entailed a sterile blood culture, FBC and differential count at the time of the AEFI with a CRP 36-48 hours later.
[¥] As per unit protocol, an infant qualified for a blood transfusion if the Haemoglobin was <8 in an infant >28 days who required non-invasive respiratory support.

## Discussion

Assessing the safety of vaccine administration in the preterm infant is complex and requires a holistic understanding of the inherent higher risk of AE already associated with prematurity.[6, 7] Overwhelming evidence demonstrates that the benefit of timely chronological vaccination far outweigh the risks of vaccination delay, even more so in the LMIC setting, and is thus strongly advocated for in this vulnerable population.[18] However, the existing higher risk of an AEFI cannot be ignored but should also not be the cause for unwarranted vaccination delays. Parental education and vaccine advocacy must be encouraged at each parent-caregiver interaction.

This study included 260 participants. The median GA of participants was 29 weeks, median birth weight 1 078 g and the median age at immunisation 44 days. Thirty-eight of the 260 participants (14.6%) experienced an AEFI with a median birth GA 28 weeks and median birth weight 988 g, median cGA of 35 weeks and a weight of 1610 g at the time of vaccination.

This study supports a significant risk of AEFI in the preterm population with a prevalence of 14.6% overall. Once all culture-confirmed and culture-negative, but probable sepsis, cases were excluded, the true prevalence of AEFI is 11.15%. Apnoea and desaturation being the commonest AEFI (figure 2) in this study, in keeping with multiple previous study findings.[9, 19, 20] The majority (89.4%) of AEFI occurred within 24 hours (figure 3), also in keeping with previous studies, as early as the 1990's.[20]

This study supports existing literature, illustrating an inverse trend in the proportion of AE (21.4%, 14.5% and 9.4%) with increasing GA (Table 2). However, in our study, this difference did not reach statistical significance as chi-square p-value was 0.26. Other additional variables investigated in this study did not individually demonstrate a statistically significant higher AEFI risk. It should be noted that no acutely unwell infant was vaccinated during this study as per the MMH unit guideline stipulated earlier.[13] Adherence to this guideline was however not audited during the study period. This conservative guideline may have consequently led to this study underestimating the prevalence of AEFI by safe-guarding against some of these described AEFI risk associations.

This study showed that a significant number of AEFI cases (28) required respiratory support, 3 needing invasive ventilation and 25 non-invasive ventilatory support (Figure 4). Only one participant with confirmed culture-positive sepsis, had a low haemoglobin (Hb) of 6.3g/dL and required a blood transfusion. Since 37/38 (97.4%) AEFI cases were deemed clinically significant, they all had a septic screen done and antibiotics commenced. A study by DeMeo et al, with a large sample size of 13 926 extremely low birth weight (ELBW) infants supports a significant increase in septic screens and the need for respiratory support (including intubation and invasive ventilation) following soon after their first vaccinations.[21]

Many studies speak of younger GA and lower weight as strongly associated with AEFI. However, studies by Gagner et al and Klein et al noted that the pathophysiological state of the infant within 24 hours of immunisation even better predicts the incidence of an AEFI.[7, 22] A study by Klein et al, showed a possible AEFI association with chronological age at immunisation <67days.[22] Of note, most studies are from countries where the first post-birth vaccination is administered at 60 days of life [23] Whereas, in South Africa, most African

countries and India, the first post-birth vaccination is given at 6-weeks of age (42 days of life). The rationale being that in LMIC the benefit of earlier vaccination for all infants outweigh the risk of serious morbidity and mortality from VPD's.[18] This younger chronological age could potentially translate to an even higher risk association.[24]

In contrast, some studies have shown no or only mild AEFI risk in preterm infants. In 2019, Tonnessen et al studied 37 preterm infants and showed a significant increase in desaturation and bradycardia events, but no significant increased risk of apnoea.[25] Locally, a study by Tooke et al found no significant AEFI in their 57 preterm in-patient infants post 6-week vaccinations.[26] Notably, these were single-centre studies with small study samples and done over short time periods.

Despite WHO and several other committee recommendations to vaccinate preterm infants at their chronological age, subsequent studies still show practice variability and unjustified vaccination delays.[7, 9] Looking at clinical practice compared to Centres for Disease Control (CDC) recommendations of vaccinating at 60 and 120 days, McKay et al noted that vaccination delays ranged between 8 days to 6 months in some cases.[9] Despite the delay, 9% still needed respiratory support post vaccination, albeit short-term only, hence this study authors' calling for formal recommendations.

The American Academy of Paediatrics (AAP) guidelines recommend monitoring hospitalised ELBW infants for significant AEFI during the 72 hours post their first vaccination [23, 27]. This is similar to previous study recommendations, Botham et al in 1997 and later by Klein et al in 2008, who recommend cardio-respiratory monitoring of all preterm infants <31weeks for a minimum 48 hours post vaccination.[22, 28, 29]

**Study Limitations**

This is a single-centre retrospective observational analysis with a relatively small study population over only two years. The cross-sectional design only allows for exploration of associations, not establishing causality and has a higher likelihood of selection, information and recall bias.

With no control group, we cannot prove that the prevalence of AEFI noted in the study differs from the prevalence of AE in the general preterm. However, co-incidental apnoea of prematurity and sepsis is less likely as the unit vaccination guideline at the time ensured that no unwell infant was vaccinated. How strictly this guideline was adhered to during the study period is not certain as no audit was done. This is another limitation to definitive results. The lack of a control group also makes statistical NNT calculations difficult and should therefore be interpreted with caution.

Our study period was relatively soon after instituting in-hospital chronological age immunisations. Human nature to resist change and a delayed acceptance of new policies, may translate to this study not representing current practice, where chronological age immunisation policies are better established.

## Conclusion

Established benefit exist in chronological vaccination of preterm infants, especially in LMICs where the burden of U5MR is predominantly due to preterm infants and VPDs. The ideal time to ensure high population uptake of vaccination is during the admission period, as giving birth has shown to be one of the most reliable points of health care globally.[30] However, we cannot ignore growing literature demonstrating the higher risk of AEFI in preterm infants.

Our study shows an 11.15% true AEFI prevalence, with 87% occurring in VPT infants and 89.4% occurring within 24 hours of vaccine administration. In view of resource constraints and constant bed pressure, yet, with the knowledge that timely chronological vaccination of preterm infants will save lives and avert associated morbidity from VPDs, our study supports a clear unit-individualised preterm immunisation protocol. The protocol should define clear clinical precautionary parameters as well as monitoring and AEFI investigation guidelines according to resource availability. We recommend at least 24 hours of cardio-respiratory or pulse oximetry monitoring for all VPT infants (<32 weeks birth GA). This could ultimately encourage timeous vaccination, remove practice discrepancies and lower the risk of potential morbidity and mortality from AEFI.

Lastly, but of equal importance, is to emphasise parental education. Caregivers should be well informed of the need for minimal 24 hour pulse-oximetry post 6 week immunisation, ensuring them that patient safety is of paramount importance. They should also be educated on VPDs and the devastating long term complications , or even death, that may present should they not vaccinate their vulnerable preterm infant.

Further prospective and larger studies with a control group and over a longer period of time is needed to strengthen our existing study.

**Acknowledgements**

We would like to acknowledge the MMH Research Committee and the Neonatal Unit HoD at the time, Dr L. Linley, for allowing and encouraging this research to be done.

Conflict of interest

The authors declare no competing interests.

Author Contributions

Primary Supervisor: Dr Anika Van Niekerk (AVN)
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Equal contribution to the output of this dissertation. AVN helped design the study proposal, analyse the data set provided by Dr Basera and editing and proof reading of the final dissertation report.

Statistician: Dr Wisdom Basera (WB)
University of Cape Town, SOPHFM: COEHR
WB has assisted with representation of results and data set analysis.

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## References


1. Chawanpaiboon S, Vogel JP, Moller A-B, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. The Lancet Global Health. 2019;7(1):e37-e46.
2. Ramokolo V, Malaba T, Rhoda N, Kauchali S, Goga A. A landscape analysis of preterm birth in South Africa: systemic gaps and solutions. South African Health Review. 2019;2019(1):133-44.
3. Sadeck LdSR, de Ávila Kfouri R. An update on vaccination in preterm infants. Jornal de Pediatria. 2023.
4. Rémy V, Zöllner Y, Heckmann U. Vaccination: the cornerstone of an efficient healthcare system. Journal of market access & health policy. 2015;3(1):27041.
5. Organization WH. World health statistics 2019: monitoring health for the SDGs, sustainable development goals. 2019.
6. Bonhoeffer J, Siegrist C-A, Heath P. Immunisation of premature infants. Archives of disease in childhood. 2006;91(11):929-35.
7. Gagneur A, Pinquier D, Quach C. Immunization of preterm infants. Human vaccines & immunotherapeutics. 2015;11(11):2556-63.
8. Fortmann MI, Dirks J, Goedicke-Fritz S, Liese J, Zemlin M, Morbach H, et al., editors. Immunization of preterm infants: current evidence and future strategies to individualized approaches. Seminars in Immunopathology; 2022: Springer.
9. McKay S, Sargent C, Domonoske C, McKay K, Duncan A. Immunization Practices and Adverse Events Following Vaccination in Infants Admitted to The Neonatal Intensive Care Unit. Annals of Neonatology Journal. 2020;2(2):60-77.
10. Sahoo T, Gulla KM, Verma S. Vaccination in preterm infants: An Indian prospective. Indian Journal of Child Health. 2020;7(1):1-7.
11. Bohnhorst B, Weidlich C, Peter C, Böhne C, Kattner E, Pirr S. Cardiorespiratory events following the second routine immunization in preterm infants: risk assessment and monitoring recommendations. Vaccines. 2021;9(8):909.
12. Clifford V, Crawford NW, Royle J, Lazzaro T, Danchin M, Perrett KP, et al. Recurrent apnoea post immunisation: Informing re-immunisation policy. Vaccine. 2011;29(34):5681-7.
13. Linley L. MMH Neonatal Nursery Preterm vaccination programme Department of Neonatology Mowbray Maternity Hospital; 2015. p. 1-2.
14. Organization WH. Global manual on surveillance of adverse events following immunization. 2014.
15. Organization WH. Global vaccine safety blueprint 2.0 (GVSB2. 0) 2021-2023. 2021.
16. Pourcyrous M, Korones SB, Arheart KL, Bada HS. Primary immunization of premature infants with gestational age< 35 weeks: cardiorespiratory complications and C-reactive protein responses associated with administration of single and multiple separate vaccines simultaneously. The Journal of pediatrics. 2007;151(2):167-72.
17. Balkundi D, Nycyk J, Cooke R. Immunisation and C reactive protein in infants on neonatal intensive care units. Archives of Disease in Childhood Fetal and Neonatal edition. 1994;71(2):F149.
18. Nakatudde I, Rujumba J, Namiiro F, Sam A, Mugalu J, Musoke P. Vaccination timeliness and associated factors among preterm infants at a tertiary hospital in Uganda. PloS one. 2019;14(9):e0221902.
19. Pfister RE, Aeschbach V, Niksic-Stuber V, Martin BC, Siegrist C-A. Safety of DTaP-based combined immunization in very-low-birth-weight premature infants: frequent but mostly benign cardiorespiratory events. The Journal of pediatrics. 2004;145(1):58-66.

20. Botham S, Isaacs D. Incidence of apnoea and bradycardia in preterm infants following triple antigen immunization. Journal of paediatrics and child health. 1994;30(6):533-5.
21. DeMeo SD, Raman SR, Hornik CP, Wilson CC, Clark R, Smith PB. Adverse events after routine immunization of extremely low-birth-weight infants. JAMA pediatrics. 2015;169(8):740-5.
22. Klein NP, Massolo ML, Greene J, Dekker CL, Black S, Escobar GJ. Risk factors for developing apnea after immunization in the neonatal intensive care unit. Pediatrics. 2008;121(3):463-9.
23. Gopal SH, Edwards KM, Creech B, Weitkamp JH. Variability in Immunization Practices for Preterm Infants. Am J Perinatol. 2018;35(14):1394-8.
24. Denizot S, Fleury J, Caillaux G, Rouger V, Rozé J-C, Gras-Le Guen C. Hospital initiation of a vaccinal schedule improves the long-term vaccinal coverage of ex-preterm children. Vaccine. 2011;29(3):382-6.
25. Tonnessen J, Urday M. Assessing the Temporality of Adverse Effects of Vaccines in the NICU. 2020.
26. Tooke L, Louw B. A successful preterm vaccination program in a neonatal unit in a developing country. Heliyon. 2019;5(11):e02857.
27. Saari TN, Diseases CoI. Immunization of preterm and low birth weight infants. Pediatrics. 2003;112(1):193-8.
28. Botham S, Isaacs D, Henderson-Smart D. Incidence of apnoea and bradycardia in preterm infants following DTPw and Hib immunization: a prospective study. Journal of paediatrics and child health. 1997;33(5):418-21.
29. Chiappini E, Petrolini C, Sandini E, Licari A, Pugni L, Mosca FA, et al. Update on vaccination of preterm infants: a systematic review about safety and efficacy/effectiveness. Proposal for a position statement by Italian Society of Pediatric Allergology and Immunology jointly with the Italian Society of Neonatology. Expert review of vaccines. 2019;18(5):523-45.
30. Chaudhari T. Vaccinations in the Newborn. Best Practice & Research Clinical Obstetrics & Gynaecology. 2020.

# Appendix A
Journal Guidelines – South African Medical Journal

**General article format/layout**

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

*SAMJ* is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

**Research**

*Guideline word limit: 4 000 words*

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

*Structured abstract*

- This should be 250-400 words, with the following recommended headings:

o **Background:** why the study is being done and how it relates to other published work.

o **Objectives:** what the study intends to find out

o **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.

o **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.

o **Conclusion:** must be supported by the data, include recommendations for further study/actions.

- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

**Appendix B**
Ethics Approval

**UNIVERSITY OF CAPE TOWN**
**Faculty of Health Sciences**
**Human Research Ethics Committee**

**Room 45 E-52-E-Floor- Old Main Building**
**Groote Schuur Hospital**
**Observatory 7925**
**Telephone** [021] 406 6492
**Email:** hrec-submissions@uct.ac.za
**Website**: www.health.uct.ac.za/fhs/research/humanethics/forms

23 June 2022

**HREC REF: 369/2022**

**Dr A Van Niekerk**
Neonatal Division
Department of Paediatrics
Red Cross War Memorial Children's Hospital
Email: anika.vanniekerk@westerncape.gov.za
Student: ptrmis001@myuct.ac.za

Dear Dr Van Niekerk

**PROJECT TITLE: THE PREVALENCE OF POST 6-WEEK IMMUNIZATION ADVERSE EFFECTS IN PRETERM INFANTS IN A BUSY NEONATAL UNIT, IN THE WESTERN CAPE, SOUTH AFRICA". IS THERE A PATTERN-**
**(MMED CANDIDATE-DR MISHKAH PETERSEN)**

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

**This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19. Please refer to guidance letter dated 02 February 2022 on our website:**
**http://www.health.uct.ac.za/fhs/research/humanethics/forms**

**Approval is granted for one year until the 30 June 2023.**

Please submit a progress form, using the standardised Annual Report Form (FHS016) if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

***The HREC acknowledge that the student: Dr Mishkah Petersen will also be involved in this study.***

**Please quote the HREC REF 369/2022 in all your correspondence.**

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

**PROFESSOR M BLOCKMAN**
**CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE**
Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

## Appendix C

Neonatal Service
Mowbray Maternity Hospital
12 Hornsey Road, Mowbray, 7700
Tel: +2721 659 5592, +27 21 6595564
Enquiries: Dr AM van Niekerk,
anika.vanniekerk@westercape.gov.za
Date: 12/02/2015

### Neonatal Nursery Preterm vaccination programme:

Preterm infants have high mortality risk from vaccine-preventable diseases (e.g. Pertussis, *H. Influenzae* and Pneumococcal disease) yet vaccination is often delayed. Earlier vaccination may reduce post discharge mortality.

All international and national guidelines recommend vaccination at chronological rather than corrected age. Studies show that most preterm infants produce protective antibodies at chronological age even if at slightly lower levels than their term infants. However, antibody production against the less immunogenic vaccine strains may be insufficient in the smallest and sickest infants.

Side effects such as fever and skin reactions are not worse than term infants.

The old Pertussis vaccine was implicated in causing apnoea in the preterm infant BUT this is NOT the case for the acellular Pertussis (aP) component vaccine that is now given in South Africa. [i]

**Recommendations for preterm infants:**

- BCG, OPV(0) – Defer until discharge.

  Note: - If HIV PCR positive: do not give BCG. (Increased risk of disseminated BCG disease or systemic BCG-itis).[ii]
  - If on TB prophylaxis/ TB treatment: defer BCG until 48hrs post stopping TB medication .

- OPV(0)- Defer to discharge (if discharged before 6wks) or give OPV(1) at 6wk immunization as per schedule.

  Note: If BCG and OPV (O) given on discharge pre 6wks of life. Please explain to parents and note in RTHC and discharge summary that the 6wks immunizations are due in 4wks time.

- All other vaccinations starting at age 6 weeks to be administered at the chronological age as per EPI schedule.

  *Regarding RV: the attenuated rotavirus used in the current generation of vaccines does not transmit (spread) easily and there is no significant risk to immune compromised patients and absolutely no staff risk.*[iii]

- If infant is acutely unwell, defer vaccinations until recovered:

*Note: Any preterm infant with ongoing cardiorespiratory events, including apnea and bradycardia or oxygen desaturation should have the 6 or 10 or 14 week immunizations deferred until there are no such episodes for 48hours AND then observed with pulse oximetry for 48hours after the immunization is given.*

Western Cape Government
Health

Neonatal Service
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Date: 12/02/2015

**Route, Dose and Recommended site of Administration of relevant Vaccines:**[iv]

| VACCINE | Form or presentation | DOSE | PREFERRED ROUTE | RECOMMENDED SITE | AGE |
|---|---|---|---|---|---|
| BCG | Powder | 0,05ml | Intradermal | Right upper arm, 1cm post to deltoid muscle insertion | Birth |
| TOPV | Liquid | Two drops | Oral | Oral | Birth & 6 weeks |
| RV | Liquid | 1.5 ml | Oral | Oral | 6 &14 weeks |
| Hep. B | Liquid | 0,5ml | Intramuscular | Lateral aspect of the right thigh in infants *under one year* | 6, 10 & 14 weeks |
| DTaP-IPV//Hib | Liquid and Powder | 0,5ml | Intramuscular | Lateral aspect of the left thigh in infants *under one year* | 6, 10 & 14 weeks<br>18 months |
| PCV | Liquid | 0,5 ml | Intramuscular | Lateral aspect of the right thigh | 6 & 14 weeks<br>9 months |

With special thanks to GSH Neonatal Division and RXH Infectious diseases Department.

[i] Groote Schuur Hospital Neonatal Division Routine Preterm vaccination Protocol, Oct2014

[ii] A.C.Hesseling, M.F.Cotton, C.Fordham von Reyn, S.M.Graham, R.P.Gie, G.D.Hussey. Union Statement: BCG in HIV-infected infants, INT J TUBERC LUNG DIS 12(12):1376–1379, 2008

World Health Organisation Information Sheet: Observed role of vaccine reactions, BCG vaccine, April 2012

[iii] Shearer WT, et al. J Allergy Clin Immunol 2014;133:961-6

[iv] Vaccinators Manual (EPI-SA) 4th edition, Oct2012

[v] Circular H 213 – 2014 Hexavalent vaccine

Dr.LLLinley, Head of Unit, Neonatology:
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## Appendix D

Western Cape Government
Health

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Neonatal Service
Date: 22/05/2021

**STANDARD OPERATING PROCEDURE**

**Neonatal Nursery Preterm vaccination programme:**

- Preterm infants are at high risk from vaccine-preventable diseases such as pertussis, Haemophilus influenzae and pneumococcal disease.
- All international and national guidelines recommend vaccination at chronological and not corrected age.
- Studies show that most preterm infants produce sufficient antibodies at chronological age even if slightly lower than their term infant counterparts.
- Side effects such as fever and skin reactions are not commoner than in term infants.
- Pertussis vaccine: only the whole cell vaccine and not the acellular pertussis vaccine (given in South Africa), was implicated in causing apnoea in preterm infants.

**MOWBRAY MATERNITY NEONATAL UNIT IN-HOSPITAL 6 & 10WEEK PRETERM VACCINATION GUIDELINE:**

**Whom to vaccinate with no delay VS when to consider a 3day to 1 week delay, as appropriate:**

NB: All NNU-admitted babies should ideally receive their 6week immunizations at or as near as possible to them being 6weeks old (chronological age).

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**WHO TO VACCINATE WITH NO DELAY, I.E. AT CHRONOLOGICAL AGE 6 WEEKS (d42) & 10WEEKS (d 70):**

**DEFINITIVE INCLUSION CRITERIA: Vaccinate timeously**

1. Stable growing prem >32wks CGA
2. Babies still on minimal respiratory support but NO Apneas/desaturation-/bradycardic episodes recorded for >48hrs (ready to discontinue respiratory support): ideally vaccinate on the respiratory support, observe minimum 24-48hrs.

**BORDERLINE: Discuss individually with consultant**

1. Stable growing prems <32wks CGA
2. *HIGH RISK PATIENT:*
   - Recent history of apnea, desaturation or bradycardia, i.e. ≤48hrs.
   - Recent LOS (≤7days) or repeated LOS episodes.
   - Very bad start to life (prolonged need for IPPV/ nCAP, respiratory support) and persistent instability.
   - Still O2 dependent (BPD) with occasional desaturations.

**DEFINITIVE EXCLUSION CRITERIA: Delay, but review within 72hrs or 1 week to vaccinate!**

1. All unstable/ ill babies
2. Babies still experiencing apneas or frequent desaturations and or bradycardic episodes, within the previous 48-72hours requiring respiratory support.
3. Babies with recent nosocomial sepsis (≤7days ago).

Aim to vaccinate ALL very preterm infants pre-discharge AND at least pre 8-weeks chronological age!

MONITORING:

- All well PRETERM INFANTS <34 weeks CGA, should ideally be on a saturation monitor from the time of immunization for at least 24 hours and still observed in hospital until 48hrs post vaccination.
- All "*HIGH RISK*" preterm infants should be monitored on a saturation monitor from the time of immunization for at least 24 hours and still observed in hospital until 48hrs post vaccination.


[i] A.C.Hesseling, M.F.Cotton, C.Fordham von Reyn, S.M.Graham, R.P.Gie, G.D.Hussey. Union Statement: BCG in HIV-infected infants, INT J TUBERC LUNG DIS 12(12):1376–1379, 2008. World Health Organisation Information Sheet: Observed role of vaccine reactions, BCG vaccine, April 2012

[ii] Shearer WT, et al. J Allergy Clin Immunol 2014;133:961-6

[iii] Chiappini E, Petrolini C, Sandini E, et al. Update on vaccination of preterm infants: a systematic review about safety and efficacy/effectiveness. Proposal for a position statement by Italian Society of Pediatric Allergology and Immunology jointly with the Italian Society of Neonatology. Expert review of vaccines. 2019;18(5):523-45.

[iv] McKay S, Sargent C, Domonoske C, et al. Immunization Practices and Adverse Events Following Vaccination in Infants Admitted to The Neonatal Intensive Care Unit. Annals of Neonatology Journal. 2020;2(2):60-7

[v] Sahoo T, Gulla KM, Verma S. Vaccination in preterm infants: An Indian prospective. Indian J Child Health. 2020; 7(1):1-7. Doi: 10.32677/IJCH.2020.v07.i01.001



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