Retrospective analysis of infection-related deaths of sudden unexpected death in infancy cases at Salt River Mortuary

by

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Declaration

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Abbreviations and symbols

%	Percent
<	Less than
=	Equal to
CMV	Cytomegalovirus
CS	Caesarean section
CSF	Cerebrospinal fluid
FAS	Foetal alcohol syndrome
FPO	Forensic Pathology Officer
FPS	Forensic Pathology Services
H&E	Haematoxylin and eosin
HAdV	Human adenovirus
HIV	Human immunodeficiency virus
HMPV	Human metapneumovirus
HPIV	Human parainfluenza virus
NHLS	National Health Laboratory Services
OAD	Office Autopsy Database
PCR	Polymerase chain reaction
PMI	Post-mortem interval
qPCR	Real-time polymerase chain reaction
RSV	respiratory syncytial virus
SIDS	Sudden infant death syndrome
SRM	Salt River Mortuary
SUDI	Sudden unexpected death in infancy

SVC	Shell vial culture
TB	Tuberculosis

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Abstract

Sudden unexpected death in infancy (SUDI) remains a global concern and is a particular burden in South Africa. Infections have been previously linked to SUDI deaths, but empirical data in a South African context is lacking. This study aimed to explore the burden and risk factors of infection-related infant death at Salt River Mortuary (SRM). To identify the types of infections associated with SUDI in a local setting, medico-legal files from SRM between 1 January 2017 and 31 December 2018 were reviewed. Included cases involved infants between 1 day and 365 days old where an infectious cause of death was either suspected or confirmed (n=288). Variables pertaining to cause of death, scope of post-mortem investigation, clinical history and risk factors were collected from case files and assessed. Most infants (73.6%) demised within four months of age. The major modifiable risk factors were co-sleeping (95.0%, n=264/278), side or prone sleeping position of the infant (73.3%, n=195/266), as well as tobacco smoke exposure (46.9%, n=122/260). Respiratory infection was the leading cause of death in this population, followed by gastroenteritis. Philippi area recorded the most gastroenteritis and respiratory infection-related deaths at 25.0% (n= 8/32) and 23.4% (n= 45/192), respectively. Milnerton and Gugulethu recorded 18.8% (n=6/32) and 15.6% (n=5/32) of gastroenteritis-related deaths, respectively. Nyanga and Mitchells Plain recorded 11.5% (n= 22/192) and 9.9% (n=19/192) of respiratory infection-related deaths, respectively. Despite infections being diagnosed as cause of death, microbial analysis was only requested in 22.9% (n= 66/288) and histology was only performed in 14.9% (n= 43/288) of the cases. Where microbial analyses were requested, *Staphylococcus aureus* bacteria was the most common organism found, followed by *Cytomegalovirus*. However, due to the small numbers of microbial analyses, geographical hotspots could not be identified at the pathogen level. There is therefore a need to adopt a standard protocol for the investigation of SUDI to optimise the translation of mortality data into targeted public health interventions. The promotion of awareness in at-risk areas should be harnessed in a local context to develop preventive strategies and ultimately reduce infant death.

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1 Background

Sudden unexpected death in infants (SUDI) describes the rapid death of a seemingly healthy infant, during the first twelve months of their life, whether the cause can be explained or not (Möllborg *et al.*, 2015). While cause of death in most SUDI cases can be determined following an exhaustive post-mortem investigation (including death scene investigation, clinical history review, and an autopsy), a subset of SUDI deaths may remain unexplained. These deaths were defined as sudden infant death syndrome (SIDS) following a diagnosis of exclusion (Krous *et al.*, 2004), therefore their validity relies on the completeness and accuracy of the post-mortem investigation (Alfelali & Khandaker, 2014, Brooks *et al.*, 2015). According to Byard (2010), death can be regarded sudden if it occurred within 24 hours of onset of symptoms and signs, or if the victim was considered generally well. Additionally, unexpected death was considered as the death of an individual who had no diseases that were regarded as being lethal therefore rendering the death unanticipated (Byard, 2010).

Due to variability between communities and their practices, precise determination of SUDI incidence was reported as being a difficult task (Byard, 2010). However, SIDS was considered the leading cause of death in infants less than one years of age in developed countries (Siren & Siren, 2011). In contrast, respiratory infections were thought to be the leading cause of infant death in developing countries (Zylbersztejn *et al.*, 2020). Epidemiological and clinicopathological studies implicate infections as the underlying basis for most SUDI deaths by overstimulating the immune system (Blackwell, 2008, Gaaloul *et al.*, 2016, Gemble *et al.*, 2020, Goldwater, 2017, Highet, Berry & Goldwater, 2009). Educational campaigns such as ‘Back to Sleep’ have led to a gradual decrease in SUDI by making the public familiar with the risks of bed-sharing and prone sleeping with regard to accidental suffocation (Hauck & Tanabe, 2008). However, SUDI still occurs in apparently healthy infants, despite being placed to sleep on their backs, indicating that there are other risk factors at play (Gemble *et al.*, 2020, Thach, 2008). Due to the paucity of research into SUDI in South Africa, little is known about these factors, which hinders interventions to reduce the high infant mortality rate (Dempers *et al*., 2018).

While there is no practical way of identifying all at-risk infants nor a solid preventive strategy yet, the first step is to identify modifiable risk factors for SUDI (Hunt & Hauck, 2006). Considering the number of SUDIs occurring each year and the trauma experienced by the parents, continued SUDI research is necessary with the overall aim of preventing and eradicating this global public health burden (Thach, 2008). This literature review will present the known risk factors for SUDI cases, and especially those which are linked to infection. It will also describe the medico-legal investigation process of SUDI cases in South Africa.

1.2 The role of infections in SUDI

The triple risk hypothesis suggested that SUDI usually occurs if a susceptible infant was exposed to an external stressor during a critical developing stage (Filiano & Kinney, 1994). Viruses were considered the most likely external stressors with factors resulting in immune deficiency and poor regulation of inflammatory mediators, thus rendering the infant susceptible to infections (La Grange *et al.*, 2014). It was also suspected that viruses increase bacterial toxins lethality by directly or indirectly interacting with the toxins and/or the host's immunoregulatory factors (La Grange *et al.*, 2014, Morris, 1999, Yagmur *et al.*, 2016). It has been reported that pathogens may not always trigger diseases; the presence of diseases may subsequently render an infant susceptible to pathogens and therefore health complications leading to death (Byard, 2010).

According to la Grange *et al*. (2014), all infants begin their life with a deficient immune system, however, not all infants are susceptible to SUDI. Addition of external risk factors such as cigarette smoke, overheating or prone sleeping could predispose the infant to infections and ultimately SUDI (Alfelali & Khandaker, 2014, Gemble *et al.*, 2020, La Grange *et al.*, 2014, Morris & Harrison, 2008). It was hypothesised that bacterial toxins of the normal microflora were common and normally encountered by infants in their early stages of life, thus infants acquire immunity to them. SUDI however, was thought to be as a result of the infant encountering a toxin-producing organism whilst having a viral infection (Morris, Haran & Smith, 1987). The disturbance of the normal nasopharyngeal bacterial flora was considered to result in bacterial overgrowth following viral respiratory tract infections. These bacteria then produce

potentially lethal toxins and may cause sudden death, often with undetectable morphological changes at autopsy (Morris, 1999). However, Byard (2010) has extensively reported autopsy approaches to detect various infections in SUDI cases.

Infections were thought to provide a pathway to SUDI through a systemic inflammatory response in infants with underdeveloped immune system (Alfelali & Khandaker, 2014, Pryce *et al.*, 2014). In addition to infections considered causative of acute diseases, some underlying diseases were thought to become lethal only if precipitated by an infection (Byard, 2010). SUDI victims were reported to have had mild fever, cough, and/or trouble feeding few days before death (Deng *et al.*, 2019, Gaaloul *et al.*, 2016). Bacterial endotoxins were considered to have resulted in sudden death via different mechanisms; for example, *Staphylococcal* superantigens and endotoxins may release cytokine that causes toxic shock while other toxins have created ion channels by inserting into cell membranes, causing swelling and cell death (Morris, 1999).

It was considered that bacterial toxins induce momentous lethal proinflammatory responses which may cause cytokine shock if not regulated (Blackwell, 2008). Cytokines are substances that help regulate the immune response upon invasion of micro-organisms, these cytokines may either proinflammatory or anti-proinflammatory (Alfelali & Khandaker, 2014). Viruses were reported to intensify cytokine activity, resulting in unregulated inflammatory mediators (La Grange *et al.*, 2014).

Goldwater (2009) hypothesised that infants may suffer a fatal episode of bacteraemia originating from the respiratory tract within the last hours of life. This may be due to inflammatory changes in the airways and lungs, where *E. coli* has been detected in lung tissues in SIDS victims (Goldwater, 2009). This was supported by Hunt and Hauck (2006) whereby they reported pulmonary congestion and pulmonary oedema in 89.0% and 63.0% of SIDS victims, respectively. In some SUDI cases, post-mortem investigation may reveal some marked inflammatory changes which were not satisfactory in explaining the cause of death (Krous *et al.*, 2004). Burger, Dempers & de Beer (2014) reported minor clinical symptoms in 29.0% of SUDI cases thus suggesting the possibility of infection in these cases.

To test the infection hypothesis, Goldwater (2009) examined the heart blood, cerebrospinal fluid (CSF), and spleen, and found potential pathogenic bacteria in 10.76% and 18.75% of victims of SIDS and infection-related deaths, respectively.

However, no potential pathogenic bacteria were found in the aforementioned sterile sites of victims of sudden accidental deaths that served as controls (Goldwater, 2009). Harris *et al*. (2012) detected pathogenic agents in 68.0% of SUDI victims, 73.0% of those pathogenic agents were documented as being the cause of death or having contributed to the cause of death. This further added support to the hypothesis that the positive findings of a pathogen, particularly in a sterile site, may represent a deadly infectious episode within the last hours before death (Goldwater, 2009, Harris *et al.*, 2012).

1.3 Risk factors and SUDI

Several risk factors have been reported to contribute towards SUDI (Mitchell, 2009). These risk factors include birth factors, external factors, sleeping environment, demographics and maternal behaviour (Alfelali & Khandaker, 2014, Möllborg *et al.*, 2015, Tangsermkijsakul, 2016, Vennemann *et al.*, 2007). SUDI was also reported to occur as a result of inter-related risk factors rather than a single overwhelming risk factor (Filiano & Kinney, 1994, L'Hoir *et al.*, 1998). Each of these will be discussed below, in relation to SUDI but also to increased susceptibility and/or the severity of infections.

1.3.1 Birth factors

Premature births refer to births before 37 weeks gestational age (Kawaguchi *et al.*, 2013). Premature infants were reported to be more susceptible to episodes of temporary breathing cessation especially in their sleep (Thach, 2008). Furthermore, Collins *et al.* (2012), reported that premature infants were three to six times more at risk of SIDS and infection-related SUDI than full-term infants. A South African study reported prematurity as one of the risk factors in 27.0% of SUDI cases (Burger, Dempers & de Beer, 2014).

Yagmur *et al*. (2016) observed that although *Cytomegalovirus* (CMV) and *Varicella zoster* virus may remain benign in most cases unless there was co-infection from other viruses, they may be fatal in premature infants due to their compromised immune

system. Prematurity was also reported as a risk factor for Group B *streptococcus* infections (Kawaguchi *et al*., 2013).

Caesarean section (CS) was considered to be associated with increased risk to SIDS mainly due to low gestational age and the lack of physical forces of labour deemed necessary for preparing the infant for the extrauterine transition (Romero *et al.*, 2006, Tribe *et al.*, 2018). Furthermore, CS was reported to reduce the exposure of the infant to maternal vaginal and intestinal flora thus altering their immune system maturation and predisposing them to infections (Goldwater, 2015, Tribe *et al.*, 2018). Vaginal delivery was therefore considered to protect against SUDI and infections by triggering the infant's immunological and physiological maturation for postnatal life (Romero *et al.*, 2006, Tribe *et al.*, 2018).

1.3.2 Sleeping environment

Bed-sharing describes the sharing of the same sleeping surface by an infant with other individuals (Vennemann *et al.*, 2007). This practice was reported to increase the risk of SIDS resulting from the obstruction of the infant's airways by the co-sleeper's body (Möllborg *et al.*, 2015). Bed-sharing was also thought to increase the infant's temperature which then led to an increase in the production of bacterial toxins in the upper respiratory tract (Mitchell, 2009, Möllborg *et al.*, 2015). A significant increase of the infant's body temperature may cause thermal stress which may lead to SUDI (Möllborg *et al.*, 2015). In addition, thermal stress may also result from covering the head of the infant or excessive bedclothes (Mitchell, 2009).

Prone sleeping was associated with SUDI as it may result in blockage of the infant's airways and eventually cause death (Mitchell, 2009). The side position was also considered unstable and therefore risky as most infants tend to roll over into a prone position (Möllborg *et al.*, 2015). While it may be considered common for healthy infants to carry *S. aureus;* however, this may produce toxins in the nasopharynx between 37°C and 40°C. Therefore, activity that raises the nasopharyngeal temperature may increase the risk to production of *S. aureus* toxins (Mitchell, 2009).

In addition to the presence of viral infections in the upper respiratory tract, the likelihood of *S. aureus* being observed in SUDI cases was increased by the infant

sleeping in a prone position (Morris & Harrison, 2008). Prone sleeping may also lead to accumulation of secretions in the upper respiratory tract which in turn may increase bacterial growth and therefore production of toxins (Alfelali & Khandaker, 2014). Furthermore, the prone position may significantly increase the nasopharyngeal temperature and thus *S. aureus* toxin production (Blackwell, 2008, Morris & Harrison, 2008).

The sleeping surface and bedding are well-established risk factors for SUDI. Soft items or materials such as duvets, pillows, and stuffed animals were considered hazardous when placed in the infant's sleeping environment (Gemble *et al.*, 2020, Tuchtan *et al.*, 2019). However, several unsuitable bedding and sleeping surfaces were identified in 25.6% of SUDI cases in a study by Tuchtan *et al*. (2019). These included makeshift beds that were unsuitable for infants, bouncy chairs, parents' bed, and sofa with cushions (Tuchtan *et al.*, 2019). Bedding that was soft and therefore had deep air pockets was also not recommended, as this prevented access to fresh air. Also, thick bedding beneath the face of a prone sleeping infant may lead to asphyxia by oxygen blockage (Thach, 2008). It was also suspected there may be protein accumulation in the foam used in cot mattresses which may be promoting bacterial growth (Alfelali & Khandaker, 2014).

1.3.3 Demographics

Male infants were 30.0% to 50.0% more likely to be affected by SUDI than female infants (Hunt & Hauck, 2006). Tuchtan *et al*. (2019) noted a significantly high number of male infants, making up 61.6% of the SUDI population they studied. This predominance was also noted by Heininger, Kleemann & Cherry (2004) whereby the male infants made up 66.1% of their SUDI population. This imbalance was suggested to be a result of female infants seemingly being more able to cope with risk factors that may impair the inflammatory responses such as exposure to cigarette smoke and the overall health of the mother during pregnancy (Alfelali & Khandaker, 2014, Pringle *et al.*, 2015).

The age of an infant was considered to be an important attribute of SIDS, with more cases recorded between two to four months and less cases recorded after six months of age (du Toit-Prinsloo *et al.*, 2011, Morris & Harrison, 2008). According to Highet,

Berry & Goldwater (2009), between two and four months of age, an infant may be temporarily hypo-immune due to the natural declining of maternal antibody levels in the infant.

Pneumocystis, a primary infection caused by the fungus *Pneumocystis jirovecii,* was more prevalent in infants between two and five months old (Vargas *et al.*, 2013). Moreover, *S. aureus* was commonly detected in the upper respiratory tract during the early weeks of life, this may be due to the bacterial mucosal carriage being highly age-dependent (Morris & Harrison, 2008).

1.3.4 Socio-economic status

Although socio-economic status is not considered a direct risk factor for SUDI, studies have shown that it may exert an influence on other risk factors for SUDI (Gemble *et al.*, 2020, Valdés-Dapena *et al.*, 1968, Zylbersztejn *et al.*, 2020). The socio-economic status of an infant may be defined by their parents' educational level, their employment position and their income (Steele, Kraus & Langworth, 1967, Vennemann *et al.*, 2007). Vennemann *et al*. (2007) reported 49.6% and 39.5% SIDS cases from low and middle socioeconomic status, respectively, while those classified as high socioeconomic status only made 10.9% of the SIDS population. Based on these findings, the conclusion was that the risk of infant death is closely correlated with socio-economic disadvantage (Vennemann *et al.*, 2007).

The socio-econonomic disadvantage was associated with increased maternal risk factors such as poor prenatal care and lower educational level, and several other risk factors such as low birth weight, smoking, and prone sleeping (Burger, Dempers & de Beer, 2014, Gemble *et al.*, 2020, Hunt & Hauck, 2006, Spencer & Logan, 2004, Valdés-Dapena *et al.*, 1968). Moreover, infants from poor families were less likey to be immunised (Zylbersztejn *et al.*, 2020). The prognosis of acute viral infections and SUDI was worse in rural areas and slums as there was lack of adequate health, proper nutrition, and diseases like human immunodeficiency virus (HIV) and malaria were more prevalent (Burger, Dempers & de Beer, 2014, Valdés-Dapena *et al.*, 1968).

Overcrowding may force bed-sharing between parents and/or other people in the household with the infant due to lack of space (Kinney & Thach, 2009). Moreover, due

to lack of funds for cribs, bed-sharing may often adopted in poor families (Kinney & Thach, 2009). Unfortunately, these may increase the occurrence of SUDI in overcrowded and poor housing conditions often observed in low socio-economic communities. Living in overcrowded households may expose the infant to respiratory tract infections, *Haemophilus influenzae* infection, tuberculosis, meningococcal disease, as well as acute rheumatic fever (Mason *et al.*, 2018, Zylbersztejn *et al.*, 2020).

The impact of socio-economic status on postnatal care was highlighted in Steele, Kraus & Langworth (1967) where there was a significant difference in knowledge of infant sleep position from parents who received counselling from health care professionals and those who did not, depending on the family's income and the medical facility they used. They further indicated that mothers who were using private health insurance received more and better counselling whereas those who were covered by the government's health system received less counselling from health care professionals and got most of their counselling from relatives and friends (Steele, Kraus & Langworth, 1967). In addition, Valdés-Dapena *et al*. (1968) reported higher numbers of SUDI cases (72.0%) from low socioeconomic status category, followed by middle and then high socioeconomic categories, with about 27.0% and 1.0% of the cases, respectively.

1.3.5 Season

The occurrence of SIDS had a seasonal distribution, with more cases being observed during colder seasons (Heininger, Kleemann & Cherry, 2004). Winter conditions may prompt the use of excessive bedding or clothing, and this may be particularly unsafe for an infant who is unwell (Mitchell, 2009). Mitchell (2009) also reported greater risk to prone sleeping position in winter than in summer.

Tuchtan *et al*. (2019) reported 61.0% of SUDI cases in winter and autumn and most of these SUDI cases were infection-related. The increased respiratory viral activity in winter also resulted in frequent occurrence of infections and influenza outbreaks which eventually played a role in the rise of SUDI occurrence (La Grange *et al.*, 2014). The increase in infections during the winter period may therefore motivate for the administration of medications to infants. However, recent use of cold medication was

deemed a contributing factor to SUDI as most cold medications are not suitable for infants (Tuchtan *et al.*, 2019).

1.3.6 Maternal factors and behaviour

Prenatal alcohol consumption results in foetal alcohol syndrome (Getahun *et al.*) and increased risk for SIDS (Kinney *et al.*, 2009, Konstat-Korzenny *et al.*, 2019). FAS was reported to result from continuous ethanol consumption, and this condition was associated with several physical and mental defects which may impair the infant's swallowing mechanism and result in fatal milk aspiration (Tangsermkijsakul, 2016). Blair *et al*. (2009) reported that alcohol consumption by parents before sleep may lead to unintentional co-sleeping. Co-sleeping with an infant while under the influence of alcohol may lead to over-laying due to the parent's reduced awareness (Goldwater, 2015). South Africa was reported to be one of the countries with high rates of FAS, with the Western Cape province recording the highest rates (Eaton *et al.*, 2012) . Choi *et al.* (2014), reported about 73.0% of pregnant women who self-reported to have used alcohol despite being aware that they were pregnant. Alcohol use in pregnant women was associated with single relationship status and younger maternal age, with median age being 28.1 years old (Brittain *et al.*, 2017, Choi *et al.*, 2014).

Prenatal exposure to cigarette smoke was identified as a risk factor for SIDS whereby in 64.0% of the cases the mother smoked cigarettes while pregnant (Vennemann *et al.*, 2007). Prenatal cigarette smoke exposure was associated with an increase in the risk of premature birth, another risk to SIDS and infection-related SUDI (Collins *et al*., 2012). Pregnant women residing in South African townships who reported to use alcohol during their pregnancies were more likely to identify as smokers, thus exposing their unborn babies to cigarrete smoke in utero (Eaton *et al.*, 2012).

Morris and Harrison (2008) showed that *E. coli* and *S. aureus* interact with nicotine to cause death thus an infant subjected to second-hand smoke was at more risk to SUDI due to bacterial infections. Second-hand cigarette smoke was also considered to increase the production of proinflammatory cytokines while suppressing the production of anti-inflammatory cytokines (Blackwell *et al.*, 2005). Overproduction of inflammatory cytokines may induce SUDI through cardiac irregularities and circulatory shock (Alfelali & Khandaker, 2014). Exposure to cigarette smoke was considered a

significant risk factor to respiratory infections in infants. This was mainly due to the cigarette smoke enhancing colonisation of potentially pathogenic bacteria and viral infections (Mitchell, 2009).

Although SIDS was considered to affect infants born from mothers of all ages and educational level; younger maternal age and low educational level was reported to be associated with the risk to SIDS (Hunt & Hauck, 2006, L'Hoir *et al.*, 1998). Younger mothers were reported to often consume alcohol and smoke, both prenatally and postnatally (Fifer *et al.*, 2009, Steele, Kraus & Langworth, 1967). While bedding use in the infant's sleeping environment was generally advised against, 77.1% of teenage mothers and 72.6% of mothers with less than a high school education were found to be using bedding (Shapiro-Mendoza *et al.*, 2015).

Steele, Kraus & Langworth (1967) reported exclusive bottle-feeding in 84.8% of the SUDI population they studied. Similarly, L'Hoir *et al*. (1998) reported 95% of their SIDS victims were exclusively bottlefed since birth. Breastmilk was considered to strengthen the infant's immune system through its effects on gut bacterial colonisation involved in the development of the immune system (Goldwater, 2015). Therefore, breast-feeding was recommended over bottle-feeding due to its protective effect against SIDS (Heininger, Kleemann & Cherry, 2004, Steele, Kraus & Langworth, 1967).

1.4 Post-mortem investigation of SUDI deaths

SUDI cases in South Africa are considered potentially unnatural by the Inquests Act 1959 (Act No. 58 of 1959) and are therefore investigated by the Forensic Pathology Services (FPS). First, the body is admitted to a medico-legal laboratory and the pathologist investigates and determines the cause of death (du Toit-Prinsloo *et al.*, 2011). At Salt River Mortuary (SRM), a full body low dose x-ray (Lodox) is performed on all cases before autopsy (Lodox® Systems (Pty) Ltd. South Africa, 2000). Based on the discretion of the investigating pathologist, the autopsy could be external, partial, or full. In a full autopsy, the body is opened, and all the organs are dissected, whereas in a partial autopsy, there is partial evisceration and dissection. A partial autopsy stops upon collection of adequate information to determine cause of death. An external autopsy however, involves only the external examination of the body (du Toit-Prinsloo *et al.*, 2011).

Should the pathologist see it necessary, samples can be collected, and either retained for further pathological or histological analyses, or sent for ancillary investigations, to determine the cause of death. The removal of any part of a body for ancillary investigations is permitted by the 'National Health Act: Regulations Regarding the Rendering of the FPS' (National Health Act No. 61 of 2003).

Samples are submitted for molecular or microbiological investigations in cases whereby the review of clinical history may indicate the involvement of an infection or if the cause of death cannot be ascertained from autopsy alone (Gaaloul *et al.*, 2016, La Grange, 2014). The National Health Laboratory Service (NHLS) offers microbial testing for different institutions including medico-legal laboratories such as Salt River Mortuary (La Grange *et al.*, 2014). Routine microbial analyses for SRM include bacteriology and virology investigations, employing bacterial culture and a respiratory viral assay, respectively. The additional microbial investigations include real-time polymerase chain reaction (qPCR)-based pathogen detection methods (Ishimirwe, 2016). However, the NHLS further uses a centrifugation enhanced shell vial culture (SVC) technique to subject every SUDI case from Tygerberg Mortuary to a routine viral screening (La Grange, 2014).

Tissue samples required for histopathological analysis include the heart, brain, liver, lungs, kidneys, and spleen; and these are routinely stained using haematoxylin and eosin (H&E) (Ishimirwe, 2016). In addition to these, cerebrospinal fluid (CSF), cardiac blood and other relevant swabs and/or tissues may be collected for bacteriology and virology investigation (Ishimirwe, 2016, La Grange, 2014). For bacterial investigations, these samples have previously been used for detection of pathogens such *S. aureus, Listeria monocytogenes, H. influenzae, Neisseria meningitidis, Streptococcus pneumoniae, and Beta haemolytic streptococcus group B* (Ishimirwe, 2016, La Grange, 2014).

Despite post-mortem microbiology being considered valuable in forensic autopsies, the quality and interpretation of post-mortem culture results have been questioned (Morris, Harrison & Partridge 2006, Riedel, 2014). The reliability of post-mortem culture was questioned due to contamination that may occur during sample collection at autopsy which meant PM cultures should be interpreted with caution (Riedel, 2014). Aseptic methods/techniques should be implemented in autopsy sample collection

process to avoid or substantially reduce the occurrence of sample contamination (Riedel, 2014, Tsokos & Püschel, 2001). It was suggested that iodine scrub of the corpse to avoid external contaminants, separate use of sterile instruments, and use of personal protective clothing of all personnel be practiced during autopsies (Morris, Harrison & Partridge 2006, Riedel, 2014, Tsokos & Püschel, 2001). Moreover, the room in which autopsy is performed should be air-controlled (Riedel, 2014). To avoid contamination of samples during collection process, it was suggested that sites should be sterilised before collecting the sample, this could be done using a searing the site of collection with a red hot spatula or flame (Morris, Harrison & Partridge 2006, Riedel, 2014). Samples collected for post-mortem culture should be immediately transported to microbiology laboratory using appropriate collection and transport media guidelines (Riedel, 2014).

Due to the blood-brain-barrier being maintained up to 24 hours after death, it was suggested that CSF and brain cultures are more reliable if contamination during sample collection can be avoided (Morris, Harrison & Partridge 2006, Tsokos & Püschel, 2001). This was concluded on the blood brain barrier protecting the aforementioned specimens from any microorganisms that may be circulating from entering both tissues (Morris, Harrison & Partridge 2006, Riedel, 2014). Although the lower-respiratory tract has been considered a sterile body site (Riedel, 2014), it has been shown that migration of bacteria present in the upper respiratory tract into the lower respiratory tract occurs more often (Morris, Harrison & Partridge 2006, Tsokos & Püschel, 2001).

The viruses cultured from liver and lung tissues from each SUDI case by the NHLS have included, but were not limited to, CMV, Human adenovirus (HAdV), Human metapneumovirus (HMPV), Human parainfluenza (HPIV) 1, 2, and 3, influenza A and B, and respiratory syncytial virus (RSV) (La Grange *et al.*, 2014). Viral detection in SUDI is influenced by factors such as optimal sampling and selection of optimal methods to be used and selection of viruses detected (La Grange *et al.*, 2014).

Although viral culture is still regarded as the gold standard for rapid detection of respiratory viruses, it is however often unsuccessful from post-mortem specimens (La Grange, 2014). La Grange (2014) reported that SVC failed to culture any of the viruses that were detected by the PCR method in post-mortem samples. However, SVC

detected most of these viruses sampled from patients in the paediatric hospital; thus, confirming its limitation in post-mortem specimens. According to La Grange (2014), this limitation is most likely attributed to factors such as post-mortem interval (PMI) and post-mortem sample integrity. In contrast, PMI did not influence the detection of respiratory viruses by PCR (La Grange, 2014). Unfortunately, due to the poor detection of certain viruses by SVC, some SUDI deaths may be incorrectly classified as SIDS whereas they had an infectious cause that may have been identified by using more sensitive detection methods (Burger, Dempers & de Beer, 2014).

The completeness of SUDI deaths investigations and thus the ancillary tests performed were often influenced by the standard autopsy protocol, budgetary constraints, and access to analytical instrumentation (Brooks *et al.*, 2015, du Toit-Prinsloo *et al.*, 2011). In South Africa, unnatural causes of death are investigated by forensic pathologists. Therefore, the forensic pathologist first determines if the referred SUDI case is natural or unnatural in manner (Tiemensma & Burger, 2012). Only unnatural deaths are mandated to be investigated by further to pinpoint the cause of death. This approach therefore leaves a gap in the knowledge of causes of death in natural SUDI cases.

Due to many SUDI cases presenting no signs of unnatural death, and often having a clinical history of mild illness, they are often classified as natural, consistent with infectious cause of death (Burger, Dempers & de Beer, 2014, du Toit-Prinsloo *et al.*, 2013). However, the presence of pathogens is not always confirmed with molecular tests in South African medico-legal mortuaries (du Toit-Prinsloo *et al.*, 2013, La Grange, 2014). Due to the lack of a specific nationally accepted standard protocol in South Africa for the investigation of SUDI cases, there is no clear scope of testing for these cases and the results obtained (du Toit-Prinsloo *et al.*, 2011). The knowledge of this information will assist in improving the investigations for these cases and also aligning the risk factors to cases with specific pathogens.

1.5 Rationale

SUDI remains a global problem in the public health due to the high death burden and South Africa is one of the countries with high rates of SUDI cases. Studies have shown that infections are common causes or contributors to SUDI deaths. Other studies have implicated several risk factors in SUDI and suspected these to be associated with the susceptibility and/or the severity of some infections.

SUDI remains a great concern not only to parents but scientists too as it has continued to evade the efforts of scientists in trying to identify at-risk infants and prevent it. By avoiding the known risk factors, many SUDI deaths could potentially be prevented (Hauck & Tanabe, 2010, Steele *et al.*). Some risk factors are modifiable and relatively easy to avoid, but these first need to be identified and then relayed to caregivers.

Currently, South Africa has no standard guideline to be used in implementing risk reduction strategies for SUDI and therefore communities do not have comprehensive knowledge of the possible interventions to reduce the risk. The implementation of this guideline depends on the understanding of the burden of infection-related SUDI and common risk factors observed in South African cases. To understand this burden, the burden of infection-related cases, the scope of post-mortem investigation and associated outcomes need to be documented. Furthermore, out of the cases in which a pathogen was identified, it should be assessed if the pathogen is associated with the geography, the demographics of the infant, maternal behaviours or other factors. Noting these risk factors and their combined effect may help identify at-risk infants and a tailored intervention can be put in place to advise caregivers accordingly. Healthcare professionals, such as midwives, could also be informed or reminded of these recommendations so they can instil them in the new mothers. These approaches may include community outreach programmes where the representative communities are educated about these pathogens and their role in SUDI, as well as how to mitigate them.

1.6 Aim and objectives

1.6.1 Aim

The aim of the study was to explore the burden and risk factors of infection related infant death at Salt River mortuary between the 1st of January 2017 and the 31st of December 2018.

1.6.2 Objectives

The objectives of this study were to:

i. Determine the number of cases admitted as SUDI and are caused by infection(s) or are infection related at SRM.
ii. Record the total number of deaths attributed to different types of infections and correlate them against geographical areas.
iii. Assess the scope of post-mortem investigations of SUDI deaths at SRM.
iv. Evaluate the risk factors in each case and assess if these are associated with types of infections

CHAPTER 2: METHODS

2.1 Study design and approvals

A quantitative, retrospective study design was employed for the purpose of this study. Case files from the Salt River Mortuary (Cape Town, South Africa) between the 1st of January 2017 and the 31st of December 2018 were reviewed. Ethical approval for this study was obtained from the Human Research Ethics Committee of the University of Cape Town (HREC REF: 248/2020) (Appendix A) and approval to access the post-mortem records was granted (Appendix B).

2.2 Data collection

The medico-legal case files relevant to this study were identified by filtering through all entries on the Office Autopsy Database (OAD) (HREC: R036/2016). Included cases consisted of those involving SUDI between 1 day and 365 days old, and where an infectious cause of death was suspected on admission or formed part of the cause of death diagnosis (n = 288).

The post-mortem records of included cases were used for collecting the variables in this study. Variables were grouped in the following categories: post-mortem investigation, ancillary tests and their results, information about the infant, the circumstances at or around the death, risk factors in the sleeping environment, as well as maternal and pregnancy risk factors. The full variable list is available in Appendix C.

The post-mortem records included (i) contemporaneous notes, a post-mortem report, written as an “Affidavit in terms of Section 212 (4), Act 51 of 1977”, interview with next of kin documented in the ‘FPS006(b) form’, which collates social and maternal history as well as circumstances surrounding and (iv) clinical history in the form of the ‘Road to Health’ clinical card. Blank copies of the FPS006(b) and the ‘Road to Health’ clinical card are available in Appendix D and E, respectively.

2.3 Data management and analysis

The data were recorded in a Microsoft Excel® for Windows (Microsoft Office, 2002) spreadsheet that was password-protected. These data were managed in accordance with the University of Cape Town data management plan. Data validation was performed to assess the accuracy, consistency, and completeness of the recorded data. Ten per cent of the case files from each year were randomly selected with the Microsoft Excel® RANDBETWEEN built-in function and the variables re-recorded in a different sheet, followed by comparison to the initially recorded data.

Residential areas were categorised according to the health sub-district as stipulated in the City of Cape Town census (*Cape Town census and population statistics: Health district profiles*, 2011) *(Appendix G).* Furthermore, the infection types derived from the general cause of death and LODOX findings were grouped to facilitate analysis. Infection types which had less than five observations were grouped into 'other' category. For the section on risk factors, data are presented out of the cases for which that variable was known. Therefore, the total number of observations varied for each variable as not all risk factors were documented in every case. A table showing the number of recorded and missing data is shown in Appendix F. Heat maps were only created for the two leading types of infections as they accounted for the majority of cases.

Microsoft Excel® and STATA version 15 (StataCorp, 2017, Stata Statistical Software Release 15. College Station, TX StataCorp LLC) were used for statistical analyses and data visualisation. The Shapiro-Wilk test was used to test for normality of the numerical variables and a Chi-square test was used for hypothesis testing of categorical variables. A p-value lower than 0.05 was considered as being statistically significant. Tableau version 2019.4 desktop professional software was used to construct heat maps (Tableau Software, Seattle, Washington, United States).

CHAPTER 3: RESULTS

3.1 Infection-related sudden unexpected death in infancy at SRM

The data gathered from the Office Autopsy Database indicated that there were 7 935 cases in total between 1 January 2017 and 31 December 2018 for which post-mortem investigations were conducted at SRM. A total of 332 cases (4.2%) were initially admitted as SUDI. Of these SUDI cases, 288 (86.7%) were attributed to, or consistent with, infectious causes following a post-mortem investigation. In the minority of these cases, there were clinical symptoms of infection, but cause of death could not be ascertained (n= 9/288, 3.1%). Infection related SUDI therefore made up 2.9% of all deaths investigated at Salt River Mortuary during the study period.

Younger infants tended to demise from infection-related SUDI, with 73.6% (212/288) of deaths less than 4 months of age. A peak was observed in infants between 1 and 2 months old (n= 82/288, 28.5%) (Figure 3.1), while neonates (<1 month old) made up 21.2% (n= 61/288) of deaths. The least number of cases was reported in infants between 10 to 11 months and 11 to 12 months old wherein each had three cases (1.0%).

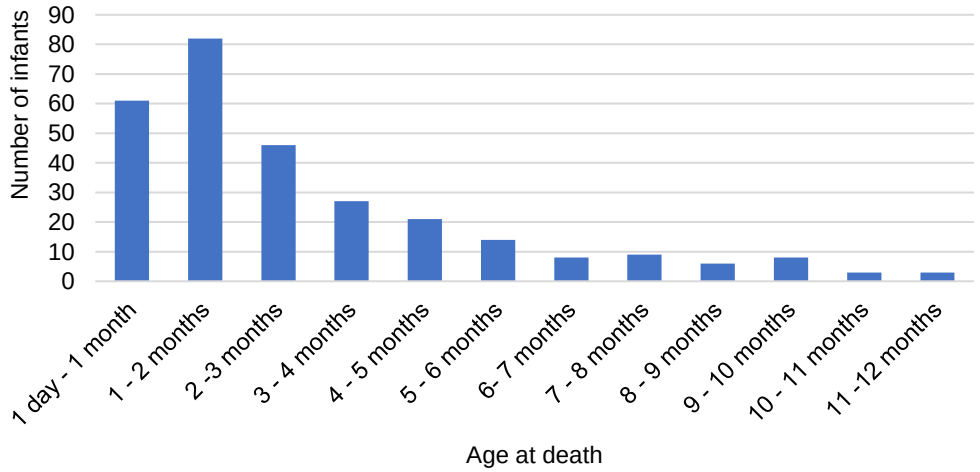

Figure 3.1: Age at death of the infants in the study cohort. There was a peak of death between 1 and 2 months with the majority of deaths (75.1%) occurring before the infant was 4 months old. Infant death then decreased from 2 to 3 months old, with the lowest number of cases recorded in 10 to 11 months and 11 to 12 months old infants.

The included infection-related SUDI cases showed a slight male predominance with 51.0% (n= 147/288). However, more female infants (n= 84/151, 55.6%) demised in 2017, whereas more male infants (n= 80/137, 58.4%) demised in 2018. When infants were grouped into neonates (<1 month old), 1 to 6 months and 6 to 12 months categories, it revealed that there were more female neonatal deaths compared to more male deaths in the 1 to 6 months category, although this was not statistically significant. The sex distribution in the 6 to 12 months age group was fairly equal (Figure 3.2).

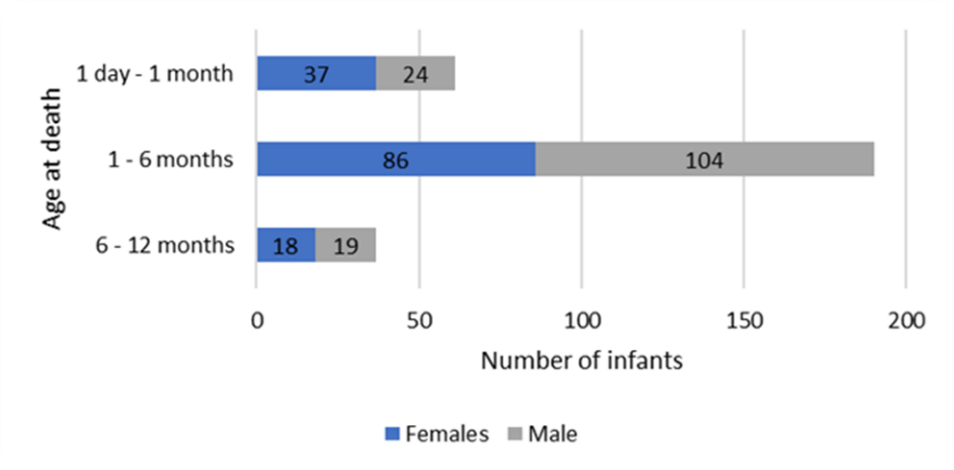

Figure 3.2: Age group by sex. More female neonates demised compared to male neonates. Above one month old, more male infant deaths were recorded compared to female infant deaths.

Infants tended to demise during the autumn and winter seasons (April to August). Although there were some observable differences in the month of death and the sex of the infant, there was no significant association between the two variables (p =0.794) (Figure 3.3).

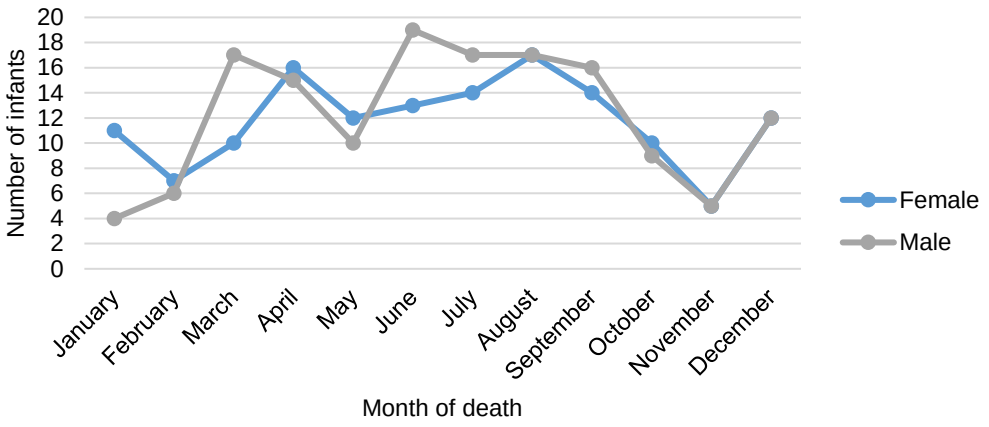

Figure 3.3: Number of infant deaths by sex in each month of death (p =0.794). More females demised in January compared to males. In contrast, more males than female demised in March and June. These differences were not statistically significant.

Most sudden infant deaths occurred in the Southern health sub-district (39.6%, n=114/288). This was followed by the Klipfontein health sub-district (26.7%, n=77/288) and the Western health sub-district (20.5%, n= 59/288) (Figure 3.4).

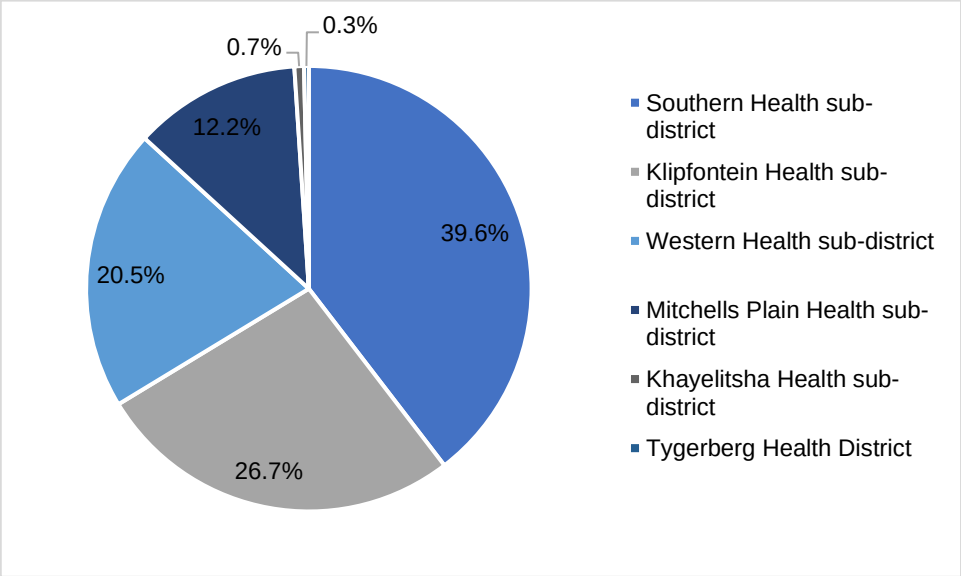

Figure 3. 4: Percentage of cases in health sub-districts. Most infant death cases occurred in the Southern health district.

3.2 Scope of post-mortem investigation

During the investigation of SUDI, the clinical history of the infant, as well as the family history are reviewed. This information is recorded in the FPS006b form and the 'Road to Health' clinic card. The FPS006b form was missing in 3.8% (n= 11/288) and incomplete in 3.1% (n= 9/288) of the cases. In 13 cases (4.5%) was the clinic card missing.

The majority of the included cases underwent an external autopsy (54.9%, n= 158/288) (Figure 3.5). A full autopsy was performed in 37.5% (n= 108/288) and partial autopsy was performed in 7.6% of the cases (n= 22/288) (Figure 3.5). In the 108 cases that underwent full autopsy, cause of death was determined at autopsy alone in 70 (64.8%), whereas the remaining causes pended ancillary investigations.

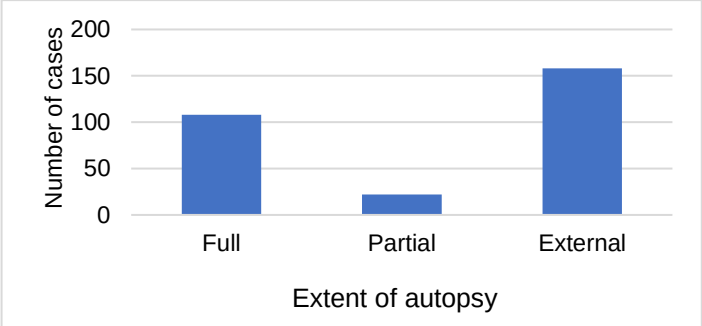

Figure 3.5: The extent of autopsy in SUDI cases. Majority of SUDI cases underwent external examination.

Full body X-ray imaging using the LODOX® X-mplar-dr imaging system (LODOX® Systems Pty (Ltd), Sandton, South Africa) was done in 96.9% (n= 279/288) of cases, regardless of the extend of autopsy. The resulting LODOX images were interpreted by the investigating forensic pathologists and the findings were included in the autopsy reports. X-ray imaging was only not performed when the facility was not working. Microbiology samples were collected, and microbial analysis requested in 22.9% (n= 66/288). Histological analysis was conducted in 14.9% (n= 43/288) of the cases. The least requested ancillary test in SUDI investigation was toxicological investigation in only 21 cases (7.3%) (Figure 3.6).

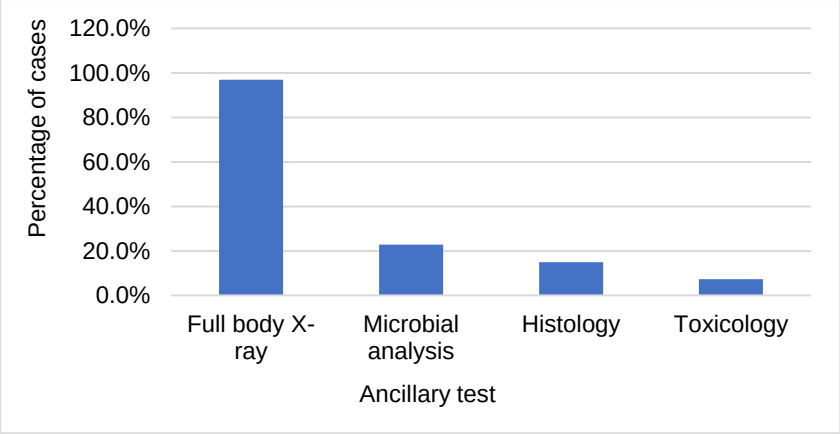

Figure 3.6: Ancillary investigations in the included cases. Full body X-ray imaging was performed in 96.9% of the cases. The least performed ancillary investigation was toxicological analysis.

3.3 Cause of death

Respiratory infections were the leading cause of infant death (n= 192/288, 66.7%) in the included cases, followed by gastroenteritis at 11.1% (n= 32/288). In a further eight infants (2.8%), both gastroenteritis and respiratory infection were diagnosed. Additionally, although infection was suspected to be the cause of death in 6.9% (n= 20/288) of the cases, the type of infection could not be specified. The cause of death in these cases was reported as natural with unspecified infectious causes. There were also nine cases (3.1%) where clinical symptoms of infection were noted at time of admission, cause of death could not be determined. Sepsis was implicated in 3.1% (n= 9/288) of the cases while several other uncommon infections were observed in 6.3% (n= 18/288) of the cases. These infections were observed in less than five cases each and included enterocolitis, malaria, urinary infection, myocarditis, and multisystem viral infection.

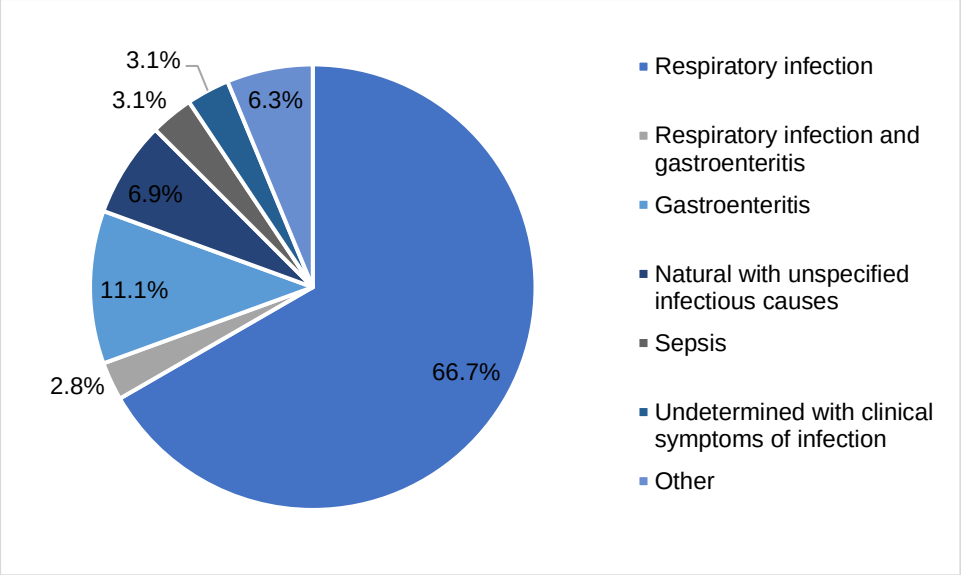

Figure 3.7: Types of infections observed in the study cohort. Respiratory infections were the cause of death in the majority of the cases, followed by gastroenteritis.

The Southern health sub-district reported more of each type of infection identified in the study. The Khayelitsha health sub-district only reported natural with unspecified infectious causes. No cases of sepsis were recorded in the Klipfontein health sub-district (Figure 3.8).

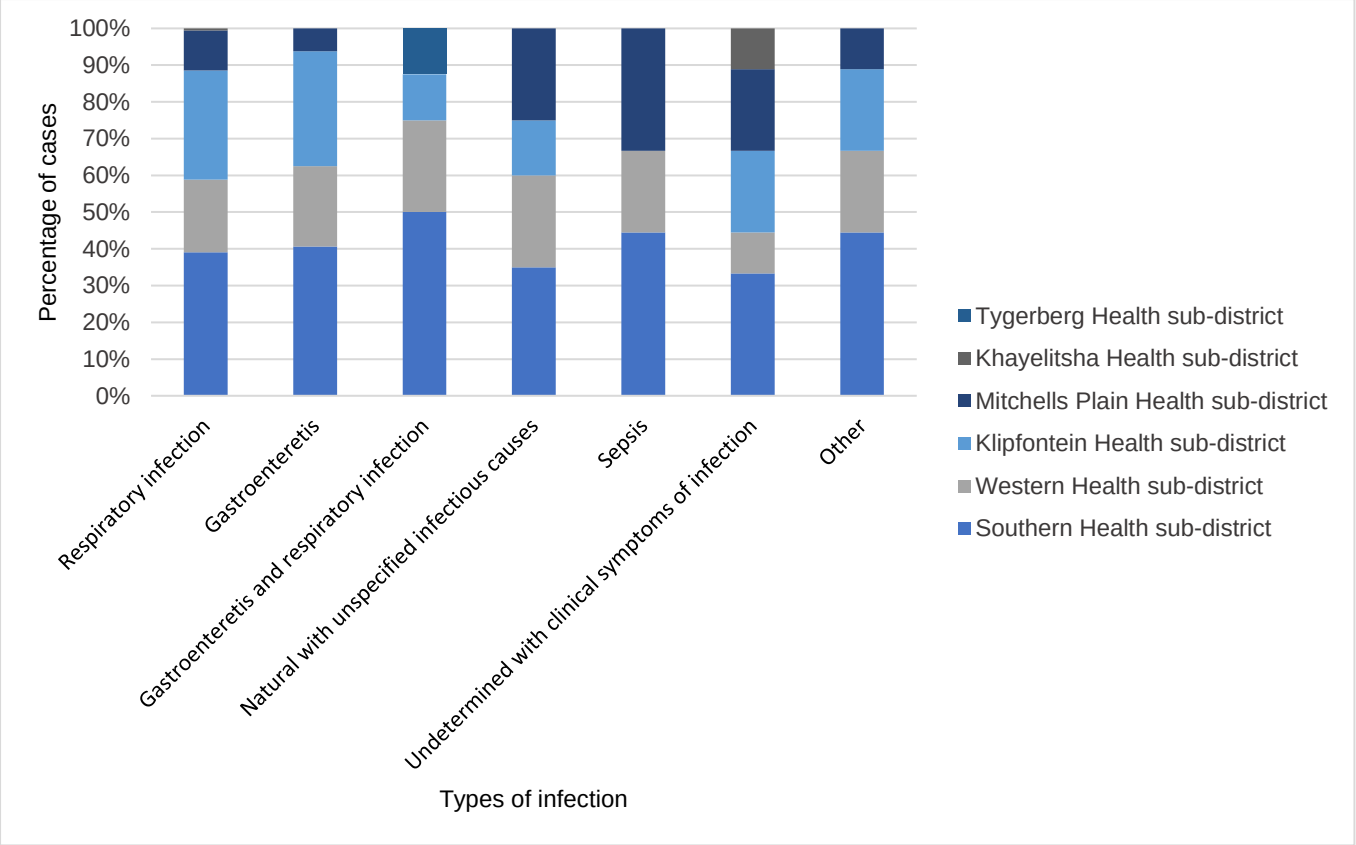

Figure 3.8: Health sub-districts with types of infection. Southern health-subdistrict recorded more of each type of infection. Klipfontein sub-health district recorded no case of sepsis.

Philippi area recorded the most respiratory infection-related SUDI cases (23.4%, n= 45/192), followed by Nyanga and Mitchells Plain at 11.5% (n= 22/192) and 9.9% (n= 19/192), respectively (Figure 3.9).

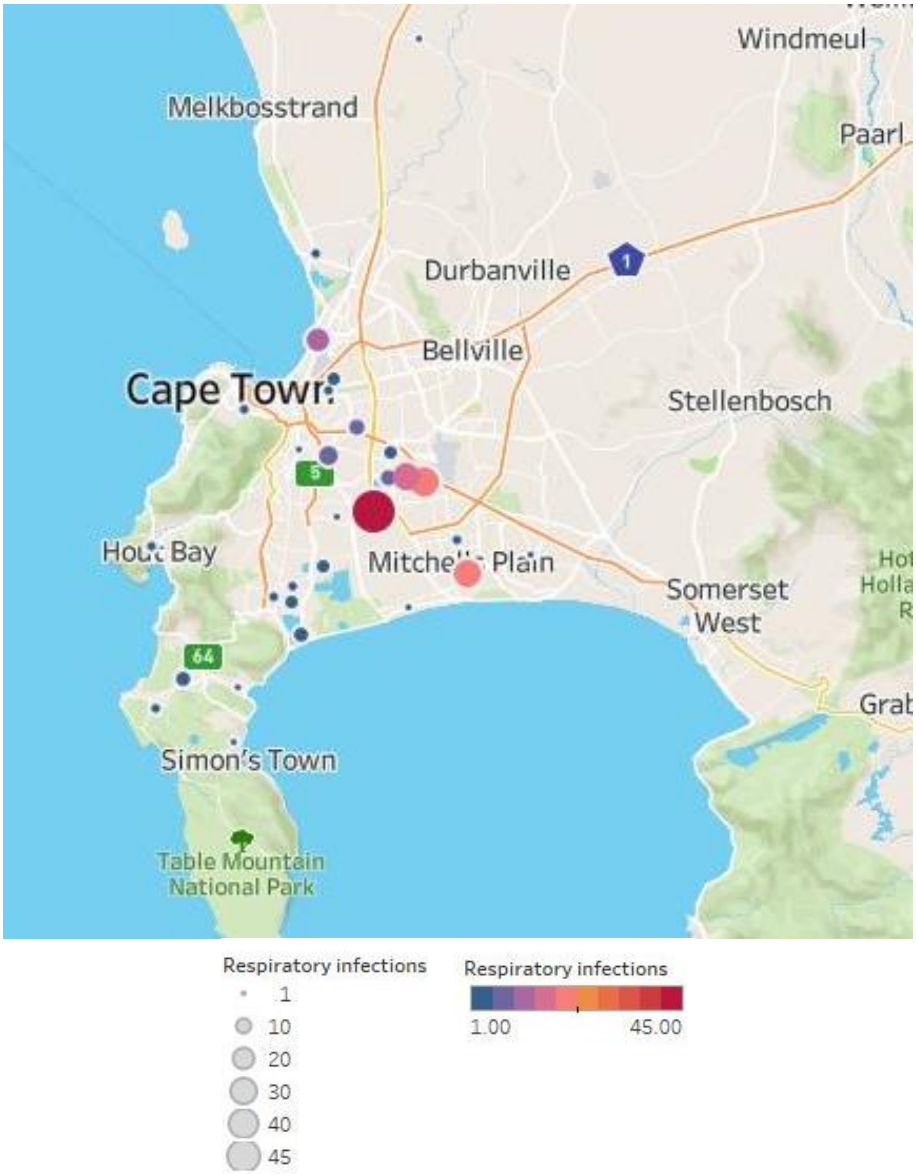

Figure 3.9: Respiratory infections per residential area of the infant. Philippi recorded the most SUDI deaths due to respiratory infections.

A quarter of gastroenteritis-related SUDI deaths was recorded in Philippi area (25.0% n= 8/32). Milnerton and Gugulethu followed with 18.8% (n= 6/32), and 15.6% (n= 5/32), respectively (Figure 3.10).

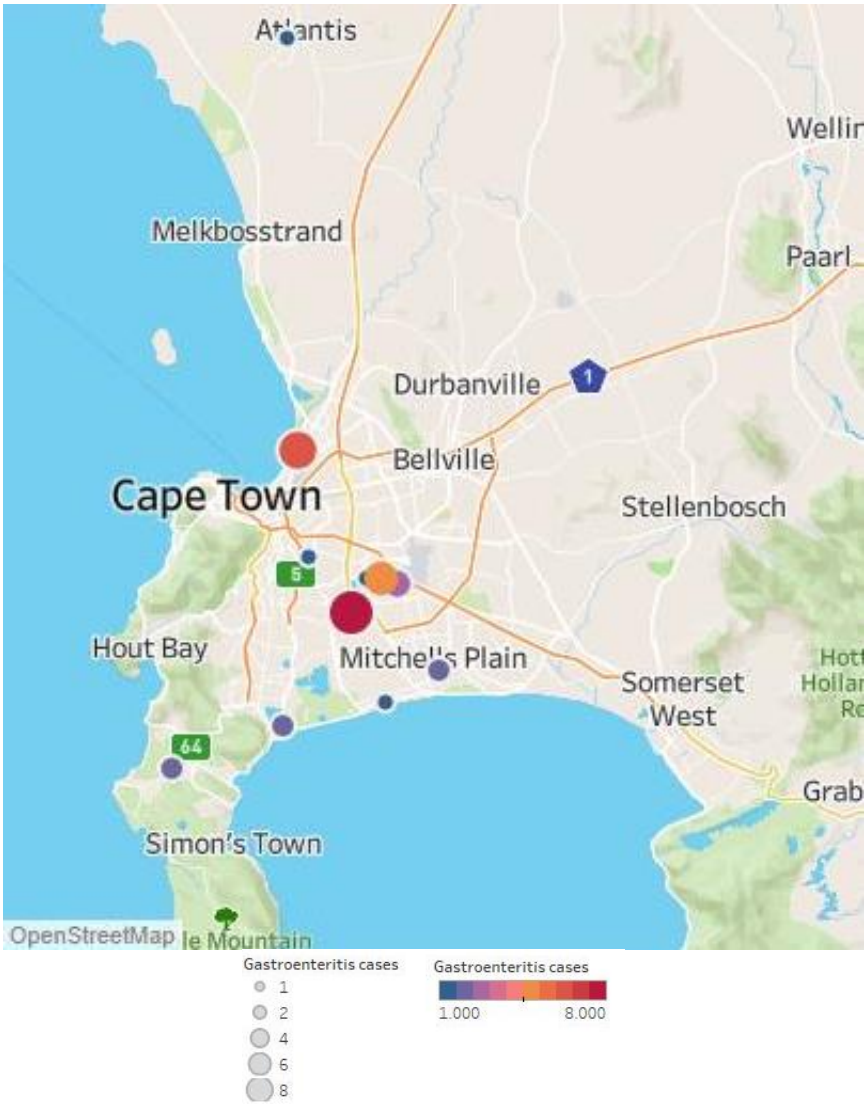

Figure 3.10: Gastroenteritis SUDI cases per residential area. Philippi recorded more gastroenteritis-related infant deaths.

Bacteria, viruses and fungi were identified during microbiological testing (Figure 3.11). Although microbiology investigations were only requested in 66 cases, bacteria were identified in 68.2% (n= 45/66) of these cases. In most cases, multiple bacteria were identified, with gram positive cocci being the most commonly identified bacteria (n= 35/104; 54.8%).

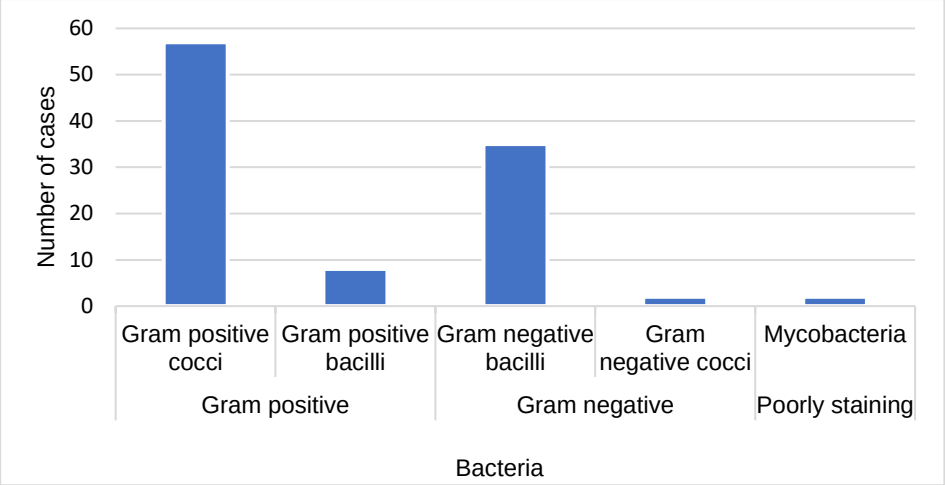

Figure 3.11: Bacteria identified in 2017 and 2018 SUDI cases at SRM. Gram positive cocci was the commonly identified bacterial category.

Fifteen different specific bacteria were identified, with the majority being present only in a single case each. Eight different viruses were detected among 15 infants. The most common specific pathogens were the *S. aureus* (26.7%, n=8/30) and *Cytomegalovirus* (53.3%, n=8/15). Fungal pathogens were only detected in three cases and all these were yeasts. Candida was the only yeast detected. (Figure 3.12)

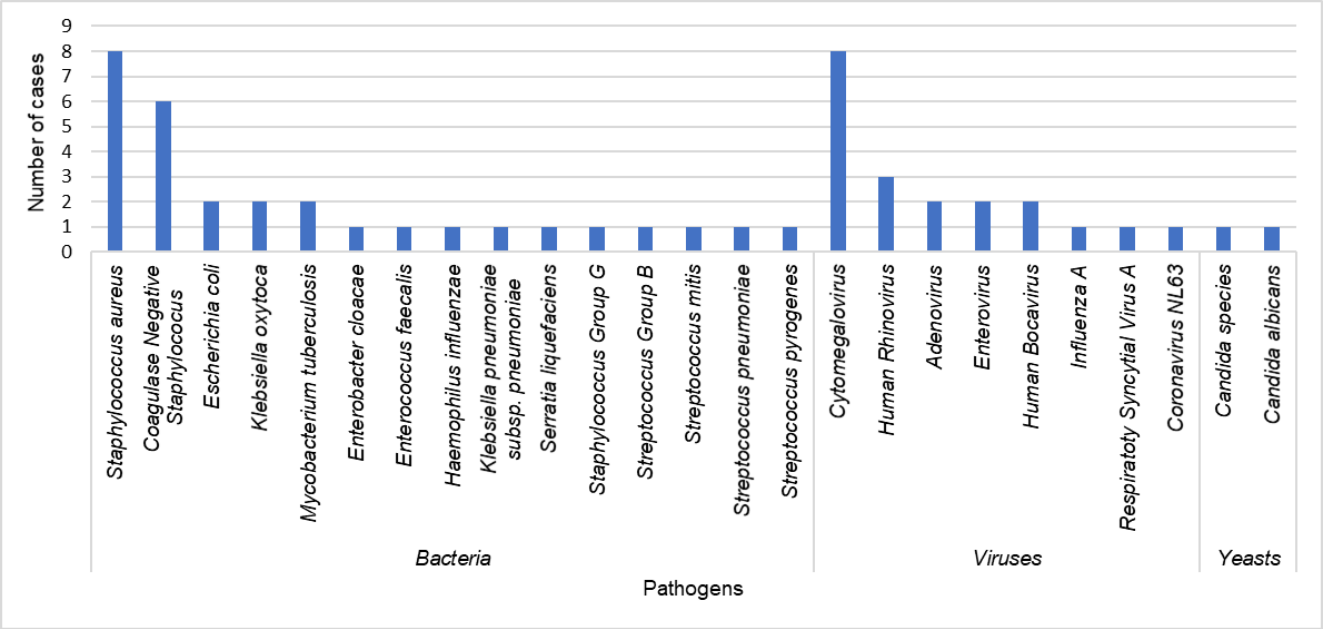

Figure 3.12: Specific pathogens isolated in the SUDI cases. *Staphylococcus* aureus and *Cytomegalovirus* were the commonly isolated pathogens.

3.4 Risk factors for infection related SUDI

Factors which have previously been found to be risk factors for SUDI and/or infection-related infant death were reviewed in this study. A comprehensive table reflecting these counts and percentages can be found in Appendix F. The key findings are presented here.

Prematurity is a well-established risk factor for SUDI and was recorded in over a third of the cases (41.9%, n= 116/277) in this study. A Chi-square test revealed a significant association between full term pregnancy and gastroenteritis (p = 0.004). Prematurity, however, was associated with sepsis (p = 0.004). Although the minority of cases were exposed to human immunodeficiency virus (HIV) (n= 66/266, 24.8%), this exposure was found to be significantly associated with gastroenteritis (p = 0.005).

The risk factor of delivery via caesarean section was only observed in 27.2% of infants, where most infants were born via normal vaginal birth (69.8%, n= 201/288). Similarly, only 4.9% (n=14/285) infants were born at home, whereas the majority were born at medical facilities such as hospitals (79.3%, n= 226/285) and clinics (15.8%, n= 45/285).

Formula feeding, also a known risk factor for infection related infant death, was observed in less than a quarter of cases (n= 66/280, 23.6%). Breastfeeding was the most common method of feeding (51.4%, n= 144/280), followed by mixed feeding (23.6%, n= 69/280). In one case was the infant never fed with milk, but tea only. Missed immunisation was identified in 34.6% (n= 88/254) of the cases.

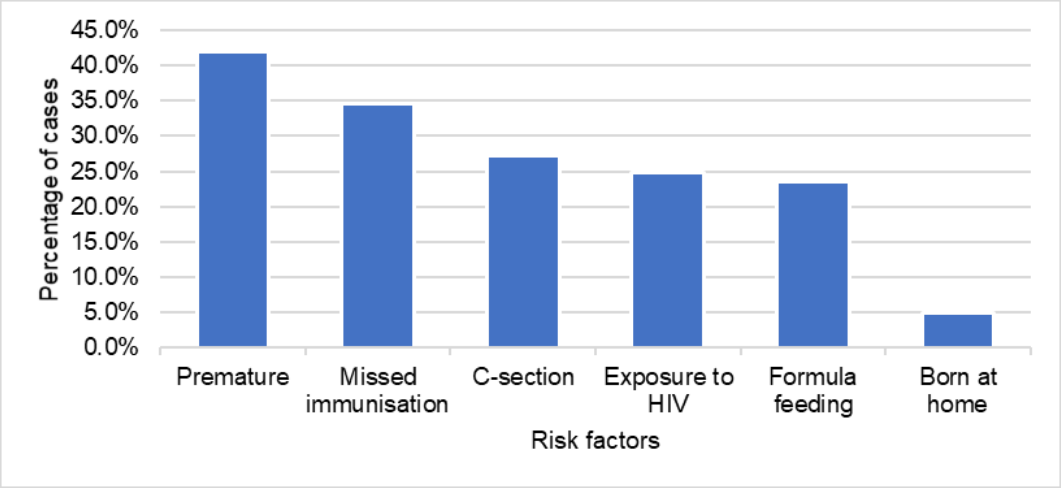

Figure 3.13: Risk factors about the infant. Prematurity was recorded in 41.9% (n= 116/277) of the cases. Full term pregnancy was associated with gastroenteritis whereas prematurity was associated with sepsis (p =0.004). Exposure to HIV was associated with gastroenteritis (p =0.005).

The major risk factor in this cohort was co-sleeping whereby in 95.0% (n= 264/278) cases the deceased shared the sleeping surface with one person or more, usually around the time of death. In 93.8% (n=180/192) of the respiratory infection cases, the infants were also reported to have been co-sleeping (*p*= 0.070). Less than one quarter of infants slept in the recommended supine position, with most infants placed to sleep on their side (48.1%, n=128/266) or prone (25.2%, n= 67/266). Foam rubber mattress, a reported risk factor for infection-related infant death, was recorded in 31.3% (n= 78/249) cases.

The type of housing the infant resided in was poorly documented, remaining undocumented in 19.4% (n=56/288) of the cases. Where reported, the majority of the infants lived in formal housing (50.9%, n= 118/232. In 40.1% (n= 93/232) of the cases, the infants lived in informal housing. Additionally, almost half of the infants (46.9%, n= 122/260) were exposed to second-hand tobacco smoke.

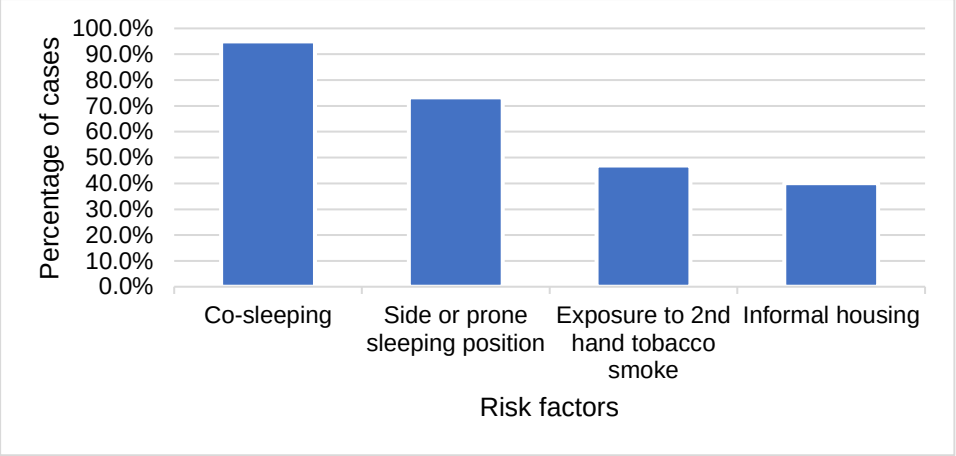

Figure 3.14: Sleeping and environment risk factors. Co-sleeping was the major risk factor, followed by risky sleeping position (side or prone). Almost half of the demised infants were exposed to second-hand tobacco smoke.

In just over a quarter of cases (n= 76/265, 28.7%), the mother reported to have smoked during the pregnancy of the deceased infant. In utero exposure to tobacco smoke was significantly associated with natural but unspecified infections (*p*= 0.013). Further, self-reported maternal alcohol consumption during pregnancy of the demised infant was observed in 14.6% (n= 39/267) of the cases. Maternal drug use was also poorly documented with this risk factor remaining undocumented in 15.3% (n= 44/288). In 67.4% of the cases, the mother was unemployed. Most of the infants who demised had mothers between 25 and 35 years old (54.0%, n=150/278).

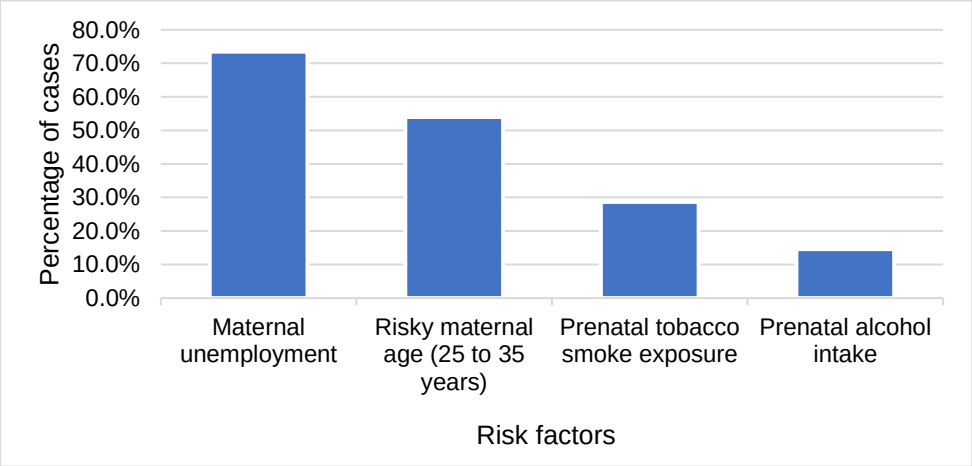

Figure 3.15: Maternal contribution and pregnancy risk factors. The mother reported to have smoked and/or consumed alcohol during the pregnancy of the deceased infant in 28.7% and 14.6%, respectively. Most infants who demised were of mothers aged between 25 and 35 years.

CHAPTER 4: DISCUSSION

4.1 The burden of infection-related SUDI

This study aimed at exploring the burden and risk factors of infection-related infant death at Salt River Mortuary. To achieve this, relevant cases were identified from autopsy records, different types of infections were documented and assessed in terms of geographical location, and risk factors were assessed in the study cohort. Infection-related SUDI at SRM made up 86.7% of the total SUDI deaths, and 3.6% of the total case load at SRM between 2017 and 2018. This is higher than the 1.8% and 2.5% reported in the Pretoria and Durban mortuaries, respectively. However, this percentage is considerably lower than the 10.3% reported in Tygerberg mortuary (du Toit-Prinsloo *et al.*, 2013).

Most infants (73.6%) demised before four months of age, with the mode at 1 to 2 months old, followed by neonates of 1 day to 1 month old (Figure 3.1). This trend was similar to that reported by La Grange *et al.* (2014), where 1 to 2 months was also the highest percentage of SUDI at Tygerberg mortuary. In Pretoria medico-legal mortuary, a peak in infant deaths was reported in 2 months old infants (du Toit-Prinsloo *et al.*, 2011). This peak observed in South African sites were earlier than those reported in other countries, where two to four months has been more prominent (Highet, Berry & Goldwater, 2009, Morris & Harrison, 2008). The peak age for SUDI between 2 and 4 months of age is thought to be explained by declining maternal antibodies in the infant, leaving the infant hypo-immune. The trend at South African mortuaries suggests that maternal antibodies decline faster in infants residing in South Africa, and thus they become immunocompromised much earlier in life. This may be influenced by genetic and environmental factors, as well as the high rates of HIV in the South African population (Diar & Velaphi, 2014, Heathfield, Martin & Ramesar, 2020, Nkosi *et al.*, 2019).

Neonatal deaths were considered to be generally rare and thus there is paucity of research in sudden unexpected death in neonates (Reyes, Somers & Chiasson, 2018). However, in this study, neonates contributed to 21.2% of deaths indicating that neonatal deaths may not be such a rare occurrence in the local setting (Figure 3.1). Further, female neonates in this cohort predominated neonatal deaths at 60.7%

(Figure 3.2), which was a similar finding to that of Reyes *et al.* (2018), who also reported a slight female predominance (52.9%) in neonatal deaths.

However, considering all cases included in this study, there was a slight male predominance (51.0%). This observation was also similar to other studies which have reported male sex to be the biological risk factor for SUDI (Harris *et al.*, 2012, Heathfield, Martin & Ramesar, 2020, Kruger, 2017, Nelson *et al.*, 2005). This has been attributed to male infants having an allegedly impaired inflammatory response (Hunt & Hauck, 2006, Pringle *et al.*, 2015). While more males demised in March and June in this study, no significant association was observed between the sex of the infant and the season of death (Figure 3.3).

Most infection-related SUDI cases were admitted to SRM during the winter season with a peak of cases recorded in August (11.8%) (Figure 3.3). La Grange (2014) also recorded a peak in SUDI deaths during winter in Tygerberg mortuary (Western, Cape). Similarly, a peak in SUDI cases was recorded in winter at the Pretoria mortuary (du Toit-Prinsloo *et al.*, 2011). This trend has also been reported internationally (Heininger, Kleemann & Cherry, 2004, Tuchtan *et al.*, 2019). This seasonal distribution of SUDI cases may be a result of the cold weather having motivated for use of excessive bedding, further increasing the risk for sudden death (Mitchell, 2009). Additionally, winter season has been linked to respiratory infections as the inhalation of cold air was reported to reduce cytokine release and cause vasoconstriction of the respiratory tract mucosa thereby increasing susceptibility to respiratory tract infections (Mourtzoukou & Falagas, 2007, Von Schirnding, Yach & Klein, 1991). Indeed, the majority of cases with respiratory infections (37.0%) were recorded in winter.

4.1.1 Respiratory-related infections

Respiratory infections were the leading cause of death in infants included in this study, with 66.7% of the cases having this diagnosis (Figure 3.7). This observation was similar to rates documented in 2014 at the same mortuary as well as at Phoenix mortuary in KwaZulu-Natal, where lower respiratory infection was the cause of death in 65.3% of infants death cases (Mathews *et al.*, 2016).

While respiratory-related infections were the leading cause of death in these cases, specific respiratory diseases were ill-defined. This was likely due to the mandate of FPS to investigate unnatural deaths only. However, where the exact disease was diagnosed, pneumonia was the most common (30.7%). This was similar to the 29.1% and 30.1% reported in Pretoria and Tygerberg mortuaries, respectively (du Toit-Prinsloo *et al.*, 2013). Similarly, international studies have also reported pneumonia as a common cause of death in infants (Mourtzoukou & Falagas, 2007, Vennemann *et al.*, 2007, Von Schirnding, Yach & Klein, 1991). Pneumonia was considered to be a result of either bacterial or viral invasion, with its mortality reported to be at peak in winter (Mourtzoukou & Falagas, 2007, Von Schirnding, Yach & Klein, 1991). This seasonality was also observed in this study where 38.5% of deaths due to pneumonia were recorded in winter.

In this study, bronchiolitis was reported in 3.1% (n=9/288) of the cases overall. However, despite bronchiolitis being considered the cause of death in these cases, no ancillary tests were requested to identify the causative pathogen. This is problematic as bronchiolitis has been considered to be linked to geographic outbreaks (Green *et al.*, 2010, Smyth & Openshaw, 2006, Zar *et al.*, 2016). The primary bronchiolitis-causing virus, RSV, was reported to vary in occurrence between different regions in South Africa (Green *et al.*, 2010, Zar *et al.*, 2016). In Gauteng, the outbreak was reported to occur between late February and August. In Cape town, the outbreak was reported between autumn and winter, whereas in KwaZulu-Natal a peak was observed between February and March (Green *et al.*, 2010).

Moreover, despite TB being a public health burden and the leading infectious cause of death in South Africa (Sumner *et al.*, 2019), TB testing was requested in only 2.1% (n= 6/288) of the cases and positive results observed in only two cases. Due to post-mortem TB test requiring lung tissue (Goldwater, 2009), the lack of testing in this study may be attributed to many of the cases having undergone external autopsy only (Figure 3.5). Also, this may be due to the FPS mandated to request further investigations only in unnatural deaths. Therefore, due to the SUDI cases included in this study diagnosed as natural, further testing may have been deemed unnecessary.

The HIV qualitative testing was also only requested in the minority of cases (3.1%) despite 24.8% of the infants reported to have been exposed to HIV (Figure 3.13).

Notably, in all the cases whereby TB test was requested, HIV qualitative test was also requested. TB and HIV were reported as the two leading communicable diseases causing death in Cape Town and Tshwane (*A tale of two cities: Mortality and causes of death in Cape Town and Tshwane*, 2014). Moreover, the prevalence of HIV and TB was reported to be high across the country (Meyer *et al.*, 2017). The burden of TB was believed to be worsened by the alarmingly increasing rates of HIV infections (Saidi, Salie & Douglas, 2017). About 15-20% of the total TB burden was reported to be made up of children; this included infants. However, due to the limited number of TB and HIV tests, the results from this study could not be used to assess the burden of TB among infection-related SUDI cases.

The common bacteria observed in this study were *S. aureus* (26.7%) and *coagulase negative staphylococcus* (20.0%) (Figure 3.12). *S. aureus* was considered one of the main pathogens that colonise the nasopharynx and cause disease and death in humans (Cimolai, 2003, Ladhani & Garbash, 2005, Venkatesh, Placencia & Weisman, 2006). These bacteria were reported to use local invasion and toxin production to cause skin infections, toxic shock syndrome, gastroenteritis and pneumonia (Jain & Daum, 1999, Ladhani & Garbash, 2005, Morris, 1999, Venkatesh, Placencia & Weisman, 2006). In contrast to *S. aureus, coagulase negative staphylococci* were considered to be non-pathogenic bacteria that colonise the human skin (Jain & Daum, 1999, Kirchhoff & Sheagren, 1985). However, they were later reported to cause diseases such as sepsis, endocarditis, and osteomyelitis (Alshaikh *et al.*, 2014, Gheybi *et al.*, 2008, Venkatesh, Placencia & Weisman, 2006).

Determining whether a positive blood culture presents a true reflection of bacteraemia or contamination has been reported to be a difficult task because contamination of blood cultures by coagulase negative staphylococci has been reported to be a common occurrence (Kirchhoff & Sheagren, 1985, Venkatesh, Placencia & Weisman, 2006). Monomicrobial growth of microorganisms typically opportunistic and/or pathogenic may be considered as being true infection (Riedel, 2014). However, it has been indicated that polymicrobial growth together with typical non-pathogenic microorganisms such as CNS and intestinal flora may more likely be during to contamination that occurred during sample collection or may be due to post-mortem artefact (Riedel, 2014, Tsokos & Püschel, 2001). However, this may not be the only indicator and therefore the results should be corroborated (Tsokos & Püschel, 2001).

Clinical history review as well as histologic examination results may also be used to corroborate microbial culture results (Morris, Harrison & Partridge 2006, Riedel, 2014,Tsokos & Püschel, 2001).

It was suggested that symptoms of infection and two positive blood cultures from two different areas on the body may be confidently reported as positive instead of contamination (Kirchhoff & Sheagren, 1985). In this study, it was not mentioned from the laboratory results if the positive results were from two separate cultures, therefore, it could not be observed if the positive results may have been a result of contamination.

In contrast to this study, La Grange reported positive bacterial results in 56.8% cases, with *Klebsiella pneumonia, E. coli,* and *S. aureus* present in 16.9%,16.2, and 5.4% of the cases, respectively. Due to limited microbial testing in this study (Figure 3.6), the observed percentages may be an inaccurate representation of the pathogens in the included SUDI cases. Therefore, a fair comparison cannot be made with the aforementioned study as they performed microbial testing in all the included cases.

4.1.2 Gastrointestinal-related infections

Gastrointestinal-related infections were the second leading cause of death in the included cases (Figure 3.7). Seasonal changes in South Africa have substantial climate variability, where significant changes in climate parameters, such as rainfall and temperature, have previously been implicated in increased thermal stress, transmission of diseases such as cholera and other diarrhoea-causing pathogens (Chersich & Wright, 2019, Mendelsohn & Dawson, 2008, Musengimana *et al.*, 2016). Musengimana *et al.* (2016) reported a significant increase in cases of diarrhoeal disease during the warm dry months (November to May) in Western Cape province in children under the age of five years. Diarrhoeal disease has remained a public concern in children under five years despite annual plans on mitigating and reducing the mortality rate due to diarrhoea (Chersich & Wright, 2019, Mendelsohn & Dawson, 2008, Musengimana *et al.*, 2016).

Although most of the infants were not tested for HIV at SRM, their clinic card or maternal history in the FPS006b was used to record whether or not they have been exposed to HIV. In 24.8%, the infants were exposed to HIV due to their mothers having

the HIV infection (Figure 3.13). In this study HIV infection was significantly associated with gastroenteritis therefore supporting the hypothesis of the negative impact of HIV on gastrointestinal immune system. Gastrointestinal immune system is known to protect against pathogens; however, its normal defences are believed to be weakened in the presence of HIV infection (Crum-Cianflone, 2010, Garcia-Prats, Ferry & Calles, 2010). This may render infants with HIV infection most likely to suffer gastrointestinal complications (Garcia-Prats, Ferry & Calles, 2010).

Mothers with infants that have been exposed to HIV should take their infants to the nearest medical facility immediately the infant vomits or has diarrhoea as these have been reported to be the main symptoms of gastrointestinal complications due to HIV infection. In addition, maternal HIV infection has also been reported to be associated with reduced immunity to other pathogens. This is due to the reduced transfer of maternal antibodies through the placenta. Therefore, infants born to HIV positive women were reported to be more vulnerable to infections as they fail to acquire passive immunity in utero (Farquhar *et al.*, 2005, Jallow *et al.*, 2017).

While only the minority of cases in this study were afforded viral testing, CMV was the most commonly detected virus (Figure 3.12). A high prevalence of CMV was previously reported in Cape Town children (Zampoli *et al.*, 2011). In contrast, at Tygerberg mortuary, the most commonly detected viruses were reported to be *Human rhinovirus*, followed by RSV (La Grange, 2014). This can be attributed to SUDI cases from Tygerberg mortuary having been subjected to SVC for viral screening whereas the selected cases in the former two studies went for qualitative PCR for CMV. CMV PCR has been praised over culture techniques as having a high degree of sensitivity thus more suitable for CMV detection (Deayton *et al.*, 2004, Dettmeyer *et al.*, 2008).

While CMV infection has been reported to be more common in infants born to mothers infected with HIV (Diar & Velaphi, 2014, Zampoli *et al.*, 2011), this was not observed in this study. Of the eight cases where CMV was detected, only in one was the infant exposed to HIV. However, due to the limited microbial testing in the included cases, it remains unknown if this relationship may have been unappreciated.

4.2 Investigation of SUDI cases

While clinical history review is deemed important in the investigation of SUDI deaths, several important sections in the FPS006b form were incorrectly documented, left undocumented or were missing. Similarly, the child death review reported that crucial data remain incomplete and as a result, in at least 16% of the cases, the cause of death remains undetermined (Mathews *et al*, 2015). According to Bennett (2018), some sections in this form remain unanswered due to language barrier between the Forensic Pathology Officer (FPO) and the infant's next-of-kin. It has therefore been suggested that the FPO interviewing the family be someone who can speak the native language of the family for better communication (Bennett, 2018).

Typically, infant cases at Salt River Mortuary undergo a full-body X-ray imaging using the X-mplar-dr imaging system (LODOX® Systems Pty (Ltd), Sandton, South Africa). Some cases were not imaged due to the facility not functioning on the day they were autopsied (Figure 3.6). The consistent use of Lodox at SRM was also reported in a study conducted on 2016 and 2017 SUDI cases whereby 98.0% of the cases underwent X-ray imaging (Bennett, Martin & Heathfield, 2020). Despite infections being suspected in 86.7% of the SUDI cases admitted between 1 January 2017 and 31 December 2018, microbial and histology analyses were requested in only 22.9% and 14.9%, respectively (Figure 3.6). Interestingly, evidence of infection was reported in all cases that underwent histological examination. It therefore remains a question of whether the same observations would have been made in the other cases had they been subjected to histology as well. The internal variation in histology and microbial analysis conducted may mainly be due to the request of ancillary tests based on the discretion of the investigating pathologist since there is no standardised protocol on investigating SUDI deaths (du Toit-Prinsloo *et al.*, 2013). Due to the limited number of microbial testing in the study cases, it is most likely that the pathogens reported in this study were grossly under-identified and therefore under-reported.

Full autopsy was not commonly performed in the SUDI cases as most of these cases presented with signs of natural diseases and most of them had a clinical history of minor illness (Figure 3.5). In the majority of the cases, cause of death was concluded

based only on a full-body X-ray and clinical history. Most of these were respiratory infections as the presence of opacities and air-bronchograms was taken as a solid evidence of respiratory infection and no further testing was deemed necessary. However, the use of radiography to diagnose infections has been criticised in other countries due to the inter and intra-observer variability in the interpretation of radiologic images (Berlin, 2007, Cherian *et al.*, 2005, Piccazzo, Paparo & Garlaschi, 2014). Also, no standardised technique or scoring system of radiograph interpretation and reporting has been established yet (Piccazzo, Paparo & Garlaschi, 2014). Due to inter and intra-observer variability, it was reported that some chest radiographs that show evidence of disease may be missed, while in other cases, the evidence may be overinterpreted as positive whereas they are actually negative for disease (Berlin, 2007). Moreover, it has been reported that it is not uncommon for individuals with TB to have a normal radiograph with positive results from TB culture (Piccazzo, Paparo & Garlaschi, 2014). It has been reported that the quality of the radiologic image may also contribute to errors in interpretation (Krupinski, 2010).

Performing a range of ancillary tests in a single case may be important as the mere presence of a pathogen does not equate to the pathogen causing the illness and eventually infant death. Therefore, in most cases, the detection of PCR viruses may have more weight if paired with evidence of infection from histology (La Grange, 2014). In this cohort however, in most cases, where histology was performed, microbial and molecular tests were not requested, and vice versa. Moreover, La Grange (2014) reported that different pathogens may be present in a single individual. This was also observed in this study whereby in several cases, more than one bacterial pathogen was identified in the same case, and in few cases, a viral and a bacterial pathogen were identified in the same case. Due to microbial analyses conducted in a small number of cases, geographical hotspots for specific pathogens could not be identified and only the types of infections could be correlated with geographic hotspots.

4.3 The importance of routine microbial testing and its impact on public health interventions in South Africa

Outbreaks of infectious diseases may be detrimental to individual health, social well-being and economy of a nation (Steele *et al.*, 2020). Routine surveillance in mortuaries by performing microbial testing routinely would ensure an early identification of outbreaks and therefore the healthcare staff and the community may be alerted as early as possible. Testing for microbes in SUDI cases may be essential particularly when a highly infectious pathogen has been isolated (Moore *et al.*, 2009). This would lead to all individuals who came into contact with the infant being tested for a diagnosis and a possible treatment administered as soon as possible to avoid familial and community outbreaks particularly in overcrowded communities (Steele *et al.*, 2020). Diagnosing and effectively treating adults who tested positive early may essentially protect the living infants and children from inhaling the infectious particles as the treatment reduces their production (Moore *et al.*, 2009).

Realising outbreaks of infectious diseases sooner may lead to better understanding of the risk factors and this will help in the management of the disease. Moreover, protocols on the management of the outbreak can be drafted as early as possible and infectious diseases may be effectively contained at a local level.

Due to limited resources in South Africa, accurately identifying disease-causing pathogens in each SUDI case using molecular and microbial testing may prove difficult. This may inadvertently lead to underappreciation of morbidity and mortality rates in infants and the community as a whole (Moore *et al.*, 2009). Moreover, outbreaks of infection may remain unreported (Dramowski *et al.*, 2015). This would lead to outbreaks of particular infections being overlooked and thus remaining unidentified and therefore the infections would continue to spread. This would lead to delayed if not absence of containment of the affected community.

The availability of resources may affect microbial testing in a mortuary setting (Steele *et al.*, 2020). With South African medico-legal mortuaries not having lots of resources, infections may be “diagnosed” via the symptom-based approach. This approach depends on good documentation of clinical history (Moore *et al.*, 2009). In this study, the clinical history was missing in 3.8% and incomplete in 3.1% of the cases. Since this approach seems to have been adopted at SRM, the FPS006b form needs to be

amended to include a section for more detailed history of infectious illnesses in the household.

4.4 Mechanisms of infection spreading

4.4.1 Geographical hotspots

In this study Philippi area recorded the most SUDI cases (23.6%), followed by Mitchells Plain at 11.1% and Nyanga in third place at 9.4%. Moreover, these three residential areas had more percentages of respiratory infections (Figure 3.9). Philippi again recorded a high number of gastroenteritis-related SUDI cases. Gugulethu and Milnerton followed in the number of SUDI cases due to gastroenteritis (Figure 3.10). Cases from the Southern and Klipfontein health sub-districts contributed 39.6% and 26.7%, respectively (Figure 3.7). While the high SUDI cases can be attributed to the Southern health sub-district being big and comprising of many residential areas, the same does not apply to the Klipfontein health sub-district. Klipfontein health sub-district is one of the smaller health sub-districts in Cape Town Metropole (*Cape Town census and population statistics: Health district profiles*, 2011) (Appendix G). Moreover, Klipfontein health sub-district was reported to be one of the two most overcrowded areas in Cape Town and this may explain the high number of infections recorded in the health sub-district despite it considered to be small (Smit, 2020).

A household may be considered overcrowded if there is more than two people per room, excluding the bathroom (Nkosi *et al.*, 2019). Overcrowding of the household could not be assessed in this study as only the number of people in dwelling was recorded and the number of habitable rooms in the household were not recorded. However, in 19.9% of the cases, more than two people were sharing a bed with the infant, thus making that sleeping environment overcrowded. It should be noted that this only describes the overcrowding in the sleeping surface environment, not that of the bedroom or the household. The type of household an individual resides was reported to have an impact on their overall health (Nkosi *et al.*, 2019). In South Africa, about 18.0% of children were reported to be living in over-crowded households, 20.0% in unsanitary households and 30.0% without access to clean tap water at home (Lake

et al., 2019). Overcrowding in families and communities also make it extremely difficult to practice social-distancing to avoid contagious disease (Nkosi *et al.*, 2019).

Overcrowding was reported to be associated with TB, diarrhoea, pneumonia and other acute respiratory infections (da Fonseca Lima *et al.*, 2016, Harling & Castro, 2014, Kristensen & Olsen, 2006, Nkosi *et al.*, 2019). Moreover, diarrhoea was reported to be more commonly observed amongst children from poor backgrounds and those residing in informal settlements as they often may lack basic services such as clean water and access to health services (Musengimana *et al.*, 2016, Nkosi *et al.*, 2019). This inadequacy in of basic needs in overcrowded areas lead to the areas commonly being hotspots for infections (Harling & Castro, 2014, Nkosi *et al.*, 2019).

In the current study, the logistics of basic services such as clean water source and access to health services were not evaluated. Therefore, no assessment of the association between the type of infections and lack of services was made. However, in 40.1% cases the demised infants lived in informal housing (Figure 3.14). Informal dwellings often lack piped water and present with mould, which may render the infant to continue living in an unhygienic environment (Nkosi *et al.*, 2019, Smit, 2020). Diseases such as TB, pneumonia, and acute lower respiratory infections have been associated with exposure to indoor air pollution (Barnes *et al.*, 2009, Harling & Castro, 2014, Nkosi *et al.*, 2019).

4.5 Risk factors

4.5.1 Modifiable risk factors

At least one modifiable risk factor was identified in each case, with most cases having more than one risk factor present. Co-sleeping was the major modifiable risk factor identified in this study as most infants slept with their parents and/or their siblings (Figure 3.14). Aside from accidental suffocation, co-sleeping has been associated with upper respiratory tract infections by increasing the infant's temperature and therefore bacterial activity (Byard, 2015). Moreover, most infants were put to sleep on their side or in a prone position (Figure 3.14). It was also observed that infants who co-slept were mostly placed to sleep on their side. The side sleeping position that has been

reported as unstable for the infant and contributory to SUDI deaths (Möllborg *et al.*, 2015).

Breastfeeding has been reported to have protective effects against sudden infant death by strengthening the immune system of the infant, and thus is a recommended type of infant feeding (Goldwater, 2015, Heininger, Kleemann & Cherry, 2004). In this study, most infants were breastfed and 92.5% of those who were breastfed co-slept. The same behaviour was demonstrated by Ball (2006) whereby breastfeeding mothers shared a bed with their infants in close proximity, regardless of the bed size. Furthermore, breastfed infants were most likely to be placed to sleep on their sides, facing the mother (Ball, 2006). While breastfeeding is recommended for the infant's wellbeing, breastfeeding mothers or new mothers who plan to breastfeed should be advised to never breastfeed while in bed to avoid falling asleep with the infant next to them. A better alternative would be to pump the breastmilk into a feeding bottle for use at night.

Of the mothers who exclusively breastfed, 76.4% were unemployed, and this was previously postulated to be due to the high cost of formula milk rather than maternal choice from knowledge of the benefits of breastfeeding (Heathfield, Martin & Ramesar, 2020). Maternal unemployment has also been implicated in influencing factors such as co-sleeping and missed immunisations and thus the overall survival of the infant (Meyer *et al.*, 2009, Vennemann *et al.*, 2007). This may mean mothers do not have transport money to take their infants for immunisations and they cannot afford to buy cots for their infants. Having mobile clinics visit areas far from general clinics at least twice a week may reduce the burden of having to use money to access basic healthcare since building a clinic for each area may prove expensive for a country like South Africa.

Prenatal and postnatal maternal smoking has been associated with socio-economic status of the mother. Meyer *et al*. (2009) demonstrated that single, unemployed mothers were more likely to smoke both prenatally and postnatally than non-single, employed counterparts. In this study 73.5% of the mothers were unemployed, and 31.4% of the unemployed mothers smoked prenatally. La Grange (2014) recorded maternal smoking in 39.0% of the cases. In this study, a higher percentage (46.9%) of second-hand exposure of the infant to cigarette smoke was recorded (Figure 3.14).

This exposure was either a result of maternal smoke or from another member of the household smoking around the infant. Prenatal smoke exposure was recorded in 28.7% of the cases and associated with unspecified infections (Figure 3.15). Prenatal smoke exposure has been reported to result in premature birth and low birth weight infants, with severity of these depending on the amount of exposure (Zhou *et al.*, 2014).

4.5.2 Birth factors

In 44.3% of infant death cases at both SRM and Phoenix mortuary, respiratory infections were associated with prematurity (Mathews S *et al.*, 2015). Comparably in this study, prematurity was associated with 46.5% of respiratory infection-related infant deaths. Foetuses acquire most of their antibodies in the last four weeks of pregnancy. Therefore, infants born before term do not acquire most of the necessary antibodies resulting in them having an underdeveloped system which cannot adequately fight against infections (Glasgow, Thompson & Ingram, 2006, Palmeira *et al.*, 2012). Of the 9 sepsis cases recorded in this study, 7 were of premature infants. This gave a statistically significant association between sepsis and prematurity (p= 0.004) and therefore premature infants are more likely to demise from sepsis than infants born at term. Understanding the development of sepsis in premature infants remain a challenge. However, maternal fever during pregnancy is thought to be associated with sepsis through intrauterine inflammation (Higgins & Silver, 2017). The child death review pilot reported that premature infants are more likely die as a result of poor home care management of pre-term infants (Mathews *et al*, 2015). However, the sample size of this statistically significant association is small so this relationship in this study may have been overestimated.

Studies have reported a gradual decrease in the rates of spontaneous vaginal birth and a rise in caesarean section births (MacDorman *et al.*, 2006, Peters *et al.*, 2018, Tribe *et al.*, 2018). Caesarean section was generally associated with impaired immune system and therefore an increased risk to infections as it was associated with a remarkable reduction of several cytokines (Milani *et al.*, 2017, Tribe *et al.*, 2018). Moreover, elective caesarean section was reported to often be performed before 39 gestation weeks, rendering the infant premature (Tita *et al.*, 2009).

In this study cohort, 66.7% of the caesarean section-born infants were premature thus supporting the hypothesis of caesarean section mode of delivery being performed before pregnancy term. The outcomes of prematurity due to caesarean section were reported to include neonatal death, sepsis, respiratory complications, as well as admission to neonatal intensive care unit (Donovan *et al.*, 2010, Getahun *et al.*, 2009, Tita *et al.*, 2009, Wylie & Mirza, 2008). However, in this study cohort, only 27.2% of the demised infants were born via the caesarean section and this mode of delivery was not significantly associated with any type of infection. This potentially excludes caesarean section as one of the major risk factors for SUDI in the local context.

The child death review pilot recommended a multi-disciplinary approach in protecting infants from SUDI (Mathews *et al*, 2015). Education of parents and caregivers (including kindergarten teachers) is a crucial part of successful awareness in reducing and preventing the occurrence of SUDI (Saidi, Salie & Douglas, 2017). Poor quality postnatal care and delayed antenatal care were reported to be associated with high neonatal mortality rate (Maredza, Chola & Hofman, 2016). Refresher training of healthcare staff can be educated then the healthcare staff can have a women's group intervention for all females to teach them about matters relating to early uptake of antenatal care, benefits of breastfeeding, sleeping practices with the infant, immunizations, hygienic disposal of children's stool and general postnatal care (Chola *et al.*, 2015, Maredza, Chola & Hofman, 2016, Saidi, Salie & Douglas, 2017). Employed mothers should be encouraged to pump their breastmilk into feeding bottles as breastmilk is thought to be protective against infection (Goldwater, 2015). This could be delivered through community-bases initiatives.

Addressing overcrowding, sanitation and lack of piped water in household could significantly improve childhood health (Lake *et al.*, 2019). Informal settlements could be upgraded in terms of housing and water source to reduce the vulnerability to infections. Moreover, low-cost housing delivery programmes could assist in de-intensifying slums and informal settlements by building multi-storey houses if there is not enough land (Smit, 2020).

4.6 Limitations

Due to the nature of this study being retrospective, some data were missing in sections of reviewed documents or in some cases the whole document. Therefore, not all variables could be recorded in all cases. This led to statistical analysis being conducted on essentially a subset of data. This limitation also highlights a need to improve the documentation process at Salt River Mortuary, which supports findings from previous studies (Bennett, Martin & Heathfield, 2020). Due to over half of the cases having underwent external autopsy, and that ancillary investigations were requested in a small percentage of the cases, this may have resulted in specific causes of death not being confirmed. Although LODOX imaging was conducted in the majority of the cases, the interpretation was conducted by forensic pathologists, and not radiologists. This might have potentially led to some important information having being missed in the images. Ancillary investigations such as histology were requested in a small percentage of the cases which also resulted in specific causes of death not being confirmed. Also, the limited microbial testing limited the ability to identify geographical hotspots and risk factors, which was one of the objectives in this study. Moreover, this study reviewed cases in only 2 years so trends of infections over time could not be assessed.

4.7 Conclusion

South Africa has a burden of infectious diseases and this may account for the burden of infection-related SUDI at SRM. Different infections require different geographic and climatic factors to thrive. This was illustrated by gastroenteritis being more common in warm and dry conditions and respiratory infections more common in the winter period. Understanding the association between climatic factors and common infections may be invaluable in preventing infection-related SUDI.

Although geographic hotspots for specific pathogens could not be specified due to small number of microbial analyses, several geographical areas have proved to be more vulnerable to SUDI than others. One of these is Philippi, which recorded more cases of respiratory infections and gastroenteritis. Nyanga, Mitchells Plain, and Milnerton areas also showed more infection-related SUDI cases. This gives a hint on

the association between the geographic location and the risk for SUDI. Moreover, the Southern and Klipfontein health sub-districts should be investigated to uncover why they have high numbers of SUDI cases.

The cases included in this study had signs of infection but only in a selected few was the inquiry into the causative agent requested. This may lead to incidences of certain infections being unrecognised and therefore outbreaks of infectious diseases. Moreover, the inconsistency observed in investigating SUDI cases further enforces the need for a nationally accepted standardised protocol for the investigation of SUDI cases to better understand the pathogens involved in this global burden. Although routine microbial and histological testing would result in more resources being utilised, they are nevertheless critical in the identification of infections and pathogens which are in the interests of public health and safety.

Due to death in SUDI often being rapid, it was noted that inflammation might not always be obvious and therefore histology may not be useful in corroborating microbial isolates. In these instances, PCR methods may be sought to corroborate the results as it was reported that microbial isolates that caused a significant disease often had dead and live microbes/toxins in the circulation and these may be amplified and ascertained (Morris, Harrison & Partridge, 2006).

This study has added to the knowledge on why and how infants die. The majority of the risk factors identified in the study, biological and modifiable, were similar to those reported in international and local literature. Unemployment remains high in the country and this has a huge impact on the occurrence of SUDI. Unemployed women seem to indulge more in alcohol and smoking, despite being pregnant. An intervention on helping women become aware of the inevitable dangers of drinking and smoking while pregnant may help in reducing this behaviour. Furthermore, maternal unemployment may play a role in lack of housing and sanitation of the household environment. Due to lack of housing and therefore space, the mother and other members of the household end up sharing the sleeping surface with the infant and this ultimately puts the infant at risk. Low-cost housing programmes may assist in building habitable houses for disadvantaged communities. Provision of clean water for these communities should also be prioritised.

Factors such as prematurity and HIV exposure are not modifiable. However, caesarean section should only be employed when clinically necessary to reduce the number of infants born before term. Early uptake of antenatal care and prioritisation of HIV testing in women attending antenatal care clinics may help reduce the chance of vertical transmission.

Proper sanitation should be upheld in medical facilities and be encouraged in all patients. Communities should be made aware on the etiquette of coughing and /or sneezing despite where they are to prevent spread of infections, particularly to infants who cannot protect themselves from these. Communities should be educated on the occurrence of SUDI and all the risk factors associated with it.

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Appendix A: Ethics approval letter

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

Room G50 -G Floor
Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 650 1236
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

27 May 2020

HREC REF: 248/2020

Dr Laura Heathfield
Division of Forensic & Toxicology
Level 5, Entrance 2
Falmouth Building
Faculty of Health Science

Dear Dr Laura Heathfield

PROJECT TITLE: RETROSPECTIVE ANALYSIS OF INFECTION RELATED DEATHS OF SUDDEN UNEXPECTED DEATH IN INFANCY CASES AT SALT RIVER MORTUARY. (MPHIL CANDIDATE: ANASTACIA MATLEBJANE)

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

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, dated 17 March 2020.

Approval is granted for one year until the 30 May 2021.

Please submit a progress form, using the standardised Annual Report Form 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)

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.

The HREC Acknowledges that the following student: Anastacia Matlebjane will also be involved in this study.

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

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
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 Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), 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 B: Approval letter to access post-mortem reports

Acting Head of Division: Division of Forensic Medicine and Toxicology

Dr Gavin Kirk

Falmouth Building
Level 1, Entrance 3
Anzio Road
Observatory
Tel: +27 (0) 21 406 6099 E-mail: gavin.kirk@uct.ac.za
Internet: www.forensicmedicine.uct.ac.za

To whom it may concern,

I, Dr Gavin Kirk, **do** hereby grant final permission for the following researchers to have access as specified for the research project as stipulated:

Principal Investigator: *Dr Laura Heathfield*
Staff number: *01426764*

Researcher: *Ms Sefule Anastacia Matlebjane*
Student number: *MTLSEF001*

Project Title: *Retrospective analysis of infection related deaths of Sudden unexpected death in infancy cases at Salt River mortuary.*

Access to:

✓	*Please tick all that apply*
	The autopsy allocations
✓	The Office Autopsy Database and related records
	Forensic Pathology Services Laboratory, Salt River for observation and collection of data
	Forensic Pathology Services Laboratory, Salt River for the collection of tissue samples
	Forensic Pathology Services Laboratory, Salt River for conducting Interviews
	Forensic Pathology Services Laboratory, Salt River for obtaining informed consent

For the data collection period of 05/05/2020 to 31/12/2020

Dr Gavin Kirk *(Signature)*

11/06/2020

Date *(dd/mm/yyyy)*

Appendix C: Table of variables

Table 1: Variables collected in the study

Variable	Type	Option
Post-mortem (PM) investigation		
Study ID #	Numerical, continuous	X
Day of PM	Categorical, nominal	Mon/Tue/Weed/Thu/Fri/Sat/Sun
Month of PM	Categorical, nominal	Jan/Feb/Mar/Apr/May/Jun/Jul/Aug/Sep/Oct/Nov/Dec
Year of PM	Numerical, discrete	2017/2018
Days to autopsy	Numerical, continuous	X days
Extent of autopsy	Categorical, ordinal	External/Partial/Full
Cause of death (COD)	Categorical, nominal	As reported
Alleged manner of death	Categorical, nominal	Accident/Homicide/Natural/Undetermined
COD undetermined at autopsy alone	Categorical, binary	Yes/No
Lodox scan conducted	Categorical, binary	Yes/No If yes, results:
Lodox findings	Categorical, nominal	As reported
Organ system affected	Categorical, nominal	Central nervous/Circulatory/Endocrine/Digestive/Integumentary/Lymphatic/Muscular/Reproductive/Respiratory/Skeletal/Urinary
Ancillary tests and results		
Histology	Categorical, binary	Yes/No
Histology results	Categorical, nominal	As reported
Toxicology samples	Categorical, nominal	As reported
Toxicology findings	Categorical, nominal	As reported
Microbiology tissue taken?	Categorical, binary	Yes/No If yes, specify:
Microbiology swabs taken?	Categorical, binary	Yes/No
Test(s) requested	Categorical, nominal	As reported
Bacterial results	Categorical, nominal	As reported
Viral results	Categorical, nominal	As reported
Fungal results	Categorical, nominal	As reported
About the infant		
Where born	Categorical, nominal	Hospital/Home/Clinic/Other If other, specify:
Delivery	Categorical, binary	Normal vaginal/C-section
Sex	Categorical, binary	Male/Female

Weeks gestation	Numerical, discrete	X weeks
Age	Numerical, continuous	(number)
Age unit	Categorical, nominal	days/weeks/months
Feeding	Categorical, nominal	Breastfeeding/Formula/Both
RTH card attached?	Categorical, binary	Yes/No
RTH vaccine set#	Categorical, ordinal	(number)
RTH card Up to date?	Categorical, binary	Yes/No
Exposure to HIV	Categorical, nominal	Yes/No
Residential area	Categorical, nominal	As reported
SAPS station	Categorical, nominal	As reported
Circumstances at or around death		
Day of death	Categorical, nominal	Mon/Tue/Wed/Thu/Fri/Sat/Sun
Month of death	Categorical, nominal	Jan/Feb/Mar/Apr/May/Jun/Jul/Aug/Sep/Oct/Nov/Dec
Year of death	Numerical, discrete	2017/2018
PM interval	Numerical, continuous	X days
Symptoms	Categorical, binary	Yes/No If yes, specify:
Medicine administered recently	Categorical, binary	Yes/No If yes, specify:
Taken to hospital	Categorical, binary	Yes/No If yes, name of hospital:
Sleeping environment (risk factors)		
Mattress type	Categorical, nominal	Foam rubber/ Inner spring/Gel/Pillow tops/Waterbed/Air bed/Latex mattresses
Sleeping position	Categorical, nominal	Back/Stomach/Side
Co-sleeping	Categorical, binary	Yes/No
# of people in bed	Numerical, discrete	(number)
Housing	Categorical, binary	Formal/Informal
Exposure to 2nd hand smoke	Categorical, binary	Yes/No
# of people in dwelling	Numerical, continuous	(number)
About the mother and pregnancy (risk factors)		
Antenatal care	Categorical, binary	Yes/No
Marital status of mother	Categorical, nominal	Married/Single/Divorced/Other If other, specify:
Age	Numerical, continuous	X years
Employment status of mother	Categorical, binary	Employed/Unemployed

Smoke prenatal	Categorical, binary	Yes/No
Drink during pregnancy	Categorical, binary	Yes/No
Drugs during pregnancy	Categorical, binary	Yes/No If yes, specify:
Previous SUDI	Categorical, binary	Yes/No If yes, how many?

FPS 006(b)

Forensic Pathology Services

SUD Questionnaire

FORENSIC PATHOLOGY SERVICE

To be completed in all individuals 5 years of age and younger who have died suddenly and unexpectedly.

FPS laboratory_____ WC _____

Name of baby _____

Part 1: Scene Questionnaire and Observations

Date:_____ **Time:**_____

Name of Forensic Pathology officer:_____

1. A: Who gives the history/ information in this case e.g. mother / father / granny / grandpa / other relative (give details)	
Name:	Relationship:
Address:	Contact telephone number:
ID Number or Date of Birth:	
1. B: Deceased's Details	
Full name:	
Home Address:	
Age:	Date of birth:
Race:	Gender:

1. C: Person(s) at/called to the scene and relationship		
Name/relationship	Date	Time
Name/relationship	Date	Time
Name/relationship	Date	Time
Police response/name	Date	Time

Paramedic response/name		Date	Time
When was the death certified/by whom		Date	Time
Was the deceased taken to hospital? If yes, provide name of hospital		Yes	No
Name of hospital: Date of arrival:	Time of Arrival:		
Name of doctor seen / declared death: (Comment: Get copies of doctors notes)			
Was the deceased's resuscitated or treated by the paramedics? If Yes, get copies of the ambulance voucher		Yes	No

1. D: Household environment at scene:

Place (dwelling) where the deceased lived at time of death:	House	Shack	Other (specify)
Number of rooms and bedrooms within household?		Bedrooms	Total rooms:
Number of individuals living in household?	Adults:	Children:	Total:

Is there enough fresh air circulating through the room in which the deceased was found?	Yes	No
Are there odours present in the room where the deceased slept? If Yes, specify	Yes	No
Was there peeling paint in the room in which the deceased slept?	Yes	No
Was the peeling paint anywhere near the deceased's food?	Yes	No
Was the room damp and/or fungal (mould) present within household?	Yes	No
Did people smoke cigarettes within the household?	Yes	No
Are there any pets in the household? If Yes, provide type and number	Yes	No

Provide a brief history of the events leading up to death:

Is there any suspicion of foul play? If Yes, please describe below	Yes	No

List items retained by FPO at scene (e.g. medications, syringes, clothing etc.)
Comments by FPO who attended scene:

Date:	Signature of deponent:

I certify that the above answers to the questionnaire at the scene was taken down by myself and that the deponent has acknowledged that he / she knows and understands the contents hereof.

Date _____ Time: _____ Place: _____

Signature of Forensic Pathology Officer: _____

Part 2: Facility Questionnaire

Date:_____ **Time:**_____

Name of Forensic Pathology officer:_____

2. A: Who gives the history/ information in this case Ideally to be provided by mother, legal guardian or primary caregiver		
Name:	Relationship:	
Address:	Contact telephone number:	
ID Number or Date of Birth:		
2. B: Deceased's Details		
Full name:		
Home Address:		
Age:	Date of birth:	
Race:	Gender:	
2. C: Circumstances of death / details about events before death		
1. When was the baby last seen alive?	Date	Time
2. Who last saw the baby alive? Name and relationship		
3. When was the baby found dead?	Date	Time
4. Who found the baby dead at the scene? Name and relationship		
5. Was the deceased's body moved when found dead? If Yes, provide details below	Yes	No
6. Was the deceased ill prior to death?	Yes	No
a) If Yes, Was the deceased taken to doctor, hospital, clinic, pharmacy or traditional healer for treatment? Indicate which option(s) and dates below	Yes	No

b) If deceased was ill and not taken to doctor or clinic, provide reasons why?					
c) Provide names of medication given to deceased (including traditional). FPO to retain all medications for pathologist.					
7. Where was the baby found dead	Bed	Cot	Couch	Floor	Other
Other:					
8. Did the baby sustain any injuries – e.g. by falling or being hit: If yes:				Yes	No
a) When did it happen?					
b) How did it happen?					
c) Where did it happen?					
d) What did the caretaker do about it?					
9. a) On what surface was the baby placed to sleep?	Bed	Couch	Cot	Floor	Other
b) Specify Other:					
c) If Bed/cot, Indicate mattress type.	Foam Rubber	Inner Spring	Other (specify):		
10.a) Was there a pillow present under the head?				Yes	No
b) If Yes, was the face pressed against pillow	Yes			No	Don't know
11.a) In what position was the deceased's body found?	Back	Stomach	Side (R/L)	Other	
b) Specify Other:					
c) In what position was the deceased's face found?	To side (R/L)	Face up	Face down	Other	
d) Specify Other:					
e) Was there anything covering the deceased's head or face?	Yes			No	Don't Know
f) If Yes, provide details.					

12. Was the head, neck or chest squashed or wedged between any objects?	Yes	No	Don't know
If Yes, provide details			
13. Did the deceased use a dummy (pacifier)?	Yes	No	Don't know
14.a) Did the deceased sleep in the same bed as the mother, father or another person?	Yes	No	Don't know
b) If Yes, describe position	In the arms	Alongside	On Chest
c) Number of people that slept in same bed with deceased?			
d) Was anyone found laying on top of deceased (overlay)?	Yes	No	Don't know
15. Did the mother or anyone in the house smoke while the deceased slept on the night/day of death?	Yes	No	Don't know
16.a) Did the mother/caregiver use alcohol before going to bed with the baby on the night/day the baby was found dead?	Yes	No	Don't Know
b) If Yes, Indicate what and how much?			
17.a) Did the mother/caregiver use drugs before going to bed with the baby on the night/day the baby was found dead?	Yes	No	Don't know
b) If Yes, Indicate what and how much			
18.a) Did the mother/caregiver give the baby medication on the night/day of death?	Yes	No	Don't know
b) If Yes, Indicate what medication and how much.			
17.a) When was the deceased last fed?		Date	Time
b) What was the deceased fed?			

2. D: About the baby

1.a) Where was the baby born?	Hospital	Clinic	Home	Other
b) Name of clinic/hospital, or specify other				
2.a) How was baby born?	Normal Vaginal delivery	Caesarian Section	Forceps or Ventouse	
b) Indicate reason for Caesarian Section or assisted delivery				
3. Birth weight		4. Birth Length		
5. Specify number of weeks gestation and indicate term	Weeks:	Preterm	Full Term	Post-dates (overdue)
6. Did the deceased receive Kangaroo care (skin to skin contact)?			Yes	No
7.a) Was the baby	Exclusively Breast fed	Exclusively Bottle fed	Mixed Bottle and Breast fed	
b) Provide name of Formula Milk				
c) Was boiling water used to make the bottle?			Yes	No
d) Provide names of any other foods used to feed deceased.				
8. Does the mother have the clinic card? If Yes, make copies for pathologist. If No, ask family to bring to facility.			Yes	No
9.a) Are the immunizations up to date for age?			Yes	No

b) If No, provide reasons				
10. Was the deceased sick before it died?	< 24 hours	1 day to 2 weeks	> 2 weeks	Never
Cold or Runny Nose				
Coughing				
Diarrhoea (Runny tummy)				
Unusually restless or irritable				
Crying more than usual				
Change in appetite or feeding				
Vomiting				
Seizures or fits				
Fever or Warm to touch				
Lethargic, floppy, no energy				
Cyanotic (Blue) or suddenly stop breathing				
11.a) Did the deceased come into contact with someone who was sick in the past 2 weeks?			Yes	No
b) if Yes, provide details of sickness and who the person was:				
12.a) Is the deceased known to be allergic to anything?	Yes	No	Unknown	
b) If yes, what?				
13.a) Did the deceased visit another province or country prior to the death?			Yes	No
b) If yes, provide details of where and when.				
14. What did the baby wear when it died? (list clothing)				

2. E: About the mother

1. Is the mother	Single	Married	In relationship
2.a) Is the mother employed?		Yes	No
b) If Yes, what works does she do?			

3. Age of the mother?		
4. What standard of schooling did she achieve?		
5.a) Is the mother the primary caregiver	Yes	No
b) If No, who is caregiver and why?		
6. Was she on contraception before she fell pregnant?	Yes	No
7. Did she take iron and vitamin tablets during her pregnancy?	Yes	No
8. Did she receive antenatal care?	Yes	No
9. Did the mother have diabetes in the pregnancy?	Yes	No
10. Did the mother have high blood pressure in pregnancy	Yes	No
11. Did the mother gain weight adequately in pregnancy?	Yes	No
12.a) Was she diagnosed with any illness during the pregnancy e.g. HIV?	Yes	No
b) If Yes, What?		
13.a) Was the mother on any medication during the pregnancy?	Yes	No
b) If yes, what medication:		
14.a) Were there any difficulties during the delivery?	Yes	No
b) If yes, what?		
15.a) Were there any problems with the baby after the delivery?	Yes	No
b) If yes, what?		
16.a) Was any specific instruction given about specific health care for the baby?	Yes	No
b) If yes, what?		
17.a) Was she depressed after the pregnancy?	Yes	No
b) If Yes, is she on any treatment?		
18.a) How many children does she have?		
b) How old are they?		
c) Do they all have the same father?	Yes	No
d) If No, provide details		
e) Do they all live with her?	Yes	No

f) If No, Provide reasons why?						
g) Are they all healthy?					Yes	No
h) If No, provide details						
i) Do any of the children have learning disability?					Yes	No
19.a) Did the mother smoke during the pregnancy?					Yes	No
b) If yes, how many cigarettes per day?						
c) Does the mother smoke after the pregnancy?					Yes	No
d) Does the mother know that smoking harms the unborn baby?					Yes	No
20.a) Did the mother drink alcohol during the pregnancy?					Yes	No
b) What did she drink?	Beer	Wine			Spirits	Other
c) Other:						
d) How often did she drink?	Daily	Weekly	Occasionally			
e) How much did she drink?						
f) Does the mother drink after the pregnancy?					Yes	No
g) Does the mother know that alcohol harms the unborn baby?					Yes	No
21.a) Did the mother use drugs?					Yes	No
b) What drugs did she use?	Cannabis	Cocaine	Heroin	Mandrax	Tik	Other
c) Other:						
d) How often does she use drugs?	Daily	Weekly	Occasionally			
22. Does the husband/partner drinks?					Yes	No
23. Do the parents of the mother drink?					Yes	No
24.a) Did the mother have a previous baby that died suddenly?					Yes	No
b) If yes, how many died?						
c) At what age did they die?						
d) Was a PM done?					Yes	No
e) If yes, Provide details as to when it was done, where it was done and what the cause of death was.						
25.a) Did the mother have a previous stillbirth?					Yes	No
b) If Yes, provide details						

2. F: Household environment				
1.a) Was the following in the room where the deceased slept to heat the room?	Electric heater	"Galley"	Fire	Other
b) Describe other:				
2. Number of people in dwelling	Adults:	Children:	Total:	
3. Estimated monthly income?				
4. Number of smokers in the dwelling?				
5. Are there mentally retarded/ challenged people in the dwelling?			Yes	No

Comments from the FPO who conducted the interview:	
List any items retained at the interview	
Date:	Signature of deponent:

I certify that the above answers to the questionnaire at the facility was taken down by myself and that the deponent has acknowledged that he / she knows and understands the contents hereof.

Date _____ Time: _____ Place: _____

Signature of Forensic Pathology Officer: _____

Department of Health
Forensic Pathology Laboratory

IMPORTANT: Always bring this booklet when you visit any health clinic, doctor or hospital

ROAD TO HEALTH GIRLS

Child's first name and surname:

Date of Birth:

DD/MM/YYYY

This booklet must be issued at birth by the health services concerned.
If birth takes place at home, the first opportunity after delivery should be used to issue the booklet.
The booklet must be issued **FREE OF CHARGE**, irrespective of delivery taking place at a public or private health facility.

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

WELL CHILD VISITS – RECORDING SHEET FOR CHILDREN

Record the following information for each visit on the spaces that are not shaded. Refer to the page numbers given in this booklet and complete the relevant section.						Remember to check the following. Tick if done, and record details on the relevant page					Date of next visit
Age	**Date**	**Growth (IMCI)** (page 14)	**PMTCT/ HIV status (IMCI)** (page 7&8)	**TB status (IMCI)**	**Feeding** (EBF/EFF/ mixed feeding for first 6 months)	Immunisations (page 6)	Vitamin A (page 9)	Deworming (page 9)	Development (page 13)	Oral Health (page 20)	
3-6 days											
6 wks											
10 wks											
14 wks											
4 mths											
5 mths											
6 mths											
7 mths											
8 mths											
9 mths											
10 mths											

Age	Date	Growth (IMCI) (page 14)	PMTCT/ HIV status (IMCI) (page 7&8)	TB status (IMCI)	Feeding (EBF/EFF/ mixed feeding for first 6 months)	Immunisations (page 6)	Vitamin A (page 9)	Deworming (page 9)	Development (page 13)	Oral Health (page 20)	Date of next visit
11mths											
12 mths											
14 mths											
16 mths											
18 mths											
20 mths											
22 mths											
24 mths											
30 mths											
36 mths											
42 mths											
48 mths											
54 mths											
60 mths											
72 mths											
12 yrs											

DETAILS OF CHILD AND FAMILY (To be completed at birth)

Child's first name and surname: _____

Child's ID number: | | | | | | | | | | | | | |

Mother's ID number: | | | | | | | | | | | | | |

Date of birth / / dd mm yyyy	Name of facility where child was born:
Child's residential address:	
Mother's name:	Mother's birth date:
Father's name:	Who does the child live with?

How many children has the mother had (including this child?)

Number born (including stillbirths) ☐	Reason(s) for death(s):
Number alive now ☐	Date information given: / / / dd mm yyyy

Child in need of special care (mark with X)
(Complete at delivery or at first contact with health services)

Is the baby a twin, triplet, etc? Yes ☐ No ☐	Does the mother need additional support to care for the child? (Specify) Yes ☐ No ☐
Any disability present (including birth defects?) (Specify) Yes ☐ No ☐	Other: (Specify)

Stamp of facility and name and signature of official who issued booklet

IMMUNISATIONS

Name and surname:

ID number:

Age group	Batch no.	Vaccine	Site	Date given dd/mm/yy	Signature
Birth		BCG	Right arm		
		OPV0	Oral		
6 weeks		OPV1	Oral		
		RV1	Oral		
		DTaP-IPV-Hib1	Left thigh		
		Hep B1	Right thigh		
		PCV 1	Right thigh		
10 weeks		DTaP-IPV-Hib2	Left thigh		
		Hep B2	Right thigh		
14 weeks		DTaP-IPV-Hib3	Left thigh		
		Hep B3	Right thigh		
		PCV2	Right thigh		
		RV2	Oral		
9 months		Measles1	Left thigh		
		PCV3	Right thigh		
18 months		DTaP-IPV-Hib4	Left arm		
		Measles2	Right arm		
6 years		Td	Left arm		
12 years		Td	Left arm		

HEAD CIRCUMFERENCE AT 14 WEEKS AND AT 12 MONTHS

14 Weeks: _____ (Range: 37 - 42 cm) **12 Months:** _____ (Range: 42 - 47.5)

REFER if head circumference is outside range

NEONATAL INFORMATION		
Birth weight:	Birth length:	Head circumference at birth:
Gestational age (weeks)	Rh factor	Mother's RPR
Antenatal (Maternal history):	Intrapartum (including mode of delivery)	
APGAR	1 min	5 min
Neonatal problems: (identify high risk problems):		
Neonatal Feeding: ☐ Exclusive breast ☐ Exclusive formula		
Special care plan / input required (e.g. Kangaroo Mother Care) Specify:		
Post-discharge plan (if baby was admitted in a neonatal ward/premature):		

PMTCT/HIV INFORMATION

Child's first name and surname:

Child's ID Number: | | | | | | | | | | | | | |

Signature of consent: _____

Date:

Fill in this section on discharge from Midwife Obstetric Unit (MOU) or obstetric ward or at first subsequent visit if not yet done

Mother's latest HIV test result	Positive	Negative	To be done
When did mother have the test?	☐ Before pregnancy	☐ During pregnancy	☐ At delivery
Is the mother on life-long ART?	Yes	No	
If yes, duration of life-long ART at time of delivery	☐ < 4 weeks	☐ > 4 weeks	☐ Before pregnancy

Document ARVs the mother received:

Did the mother receive infant feeding counseling?	Yes	No
Decision about infant feeding	☐ Exclusive breast	☐ Exclusive formula

Document Nevirapine given:

All HIV exposed infants should receive Nevirapine for a minimum of 6 weeks

Has the mother disclosed to anyone in the household?	Yes	No
Has the mother's partner been tested?	Yes	No

Remember to offer testing for all the mother's other children if not yet done

Offer a mother with unknown HIV status a rapid HIV test.
If mother's HIV rapid test is positive, perform an HIV DNA PCR test on infant if ≥ 6/52

Fill in this section if infant is HIV exposed

6 week visit

What feeds has the infant received? ☐ Exclusive breast ☐ Exclusive formula ☐ Mixed feeding

HIV PCR test done? Yes / No
Date:

Affix NHLS tracking barcoded sticker here

Cotrimoxazole started? Yes / No

Infant feeding discussed? Yes / No

Has the child received Nevirapine? Yes / No

If yes: Stop now / Continue

Stop Nevirapine if the mother is on life-long ART or the child has stopped breast-feeding. If not, continue until breastfeeding stops

10 week visit, or earlier if ill

PCR result: Positive / Negative

Post test counseling done? Yes / No

Referred for ART? Yes / No

Stop Nevirapine if PCR is positive

Cotrimoxazole given? Yes / No

Has child received Nevirapine? Yes / No

If yes: Stop now / Continue

Encourage a mother whose baby is HIV positive to continue breastfeeding

Retest HIV negative children 6 weeks after cessation of breastfeeding, or if clinical suspicion.
An HIV exposed child should be retested with a rapid HIV Antibody test at 18 months

Repeat PCR test ☐ Positive ☐ Negative
Date:

HIV antibody test ☐ Positive ☐ Negative
Date:

Post test counseling done? Yes / No

Referred for ART Yes / No

Stop Nevirapine if PCR is positive

Cotrimoxazole given? Yes / No

Has child received Nevirapine? Yes / No

If yes: Stop now / Continue

Tick if there is additional information on HIV status in clinical notes ☐

VITAMIN A SUPPLEMENTATION

	At age	Date given dd/mm/yy	Signature	At age	Date given dd/mm/yy	Signature
100 000 IU	6 mths	/ /				
200 000 IU every 6 months	12 mths	/ /		42 mths	/ /	
	18 mths	/ /		48 mths	/ /	
	24 mths	/ /		54 mths	/ /	
	30 mths	/ /		60 mths	/ /	
	36 mths	/ /				

ADDITIONAL DOSES:

For conditions such as measles, severe malnutrition, xerophthalmia and persistent diarrhoea. Omit if dose has been given in last month.
Measles and xerophthalmia: Give one dose daily for two consecutive days. Record the reason and dose given below.

Date	Dose given	Reason	Signature	Date	Dose given	Reason	Signature

DEWORMING TREATMENT (Mebendazole or Albendazole)

Dose	At age	Date given dd/mm/yy	Signature	At age	Date given dd/mm/yy	Signature
	12 mths	/ /		18 mths	/ /	
	24 mths	/ /		48 mths	/ /	
	30 mths	/ /		54 mths	/ /	
	36 mths	/ /		60 mths	/ /	
	42 mths	/ /				

HEALTH PROMOTION MESSAGES

Up to 6 months

Feeding:

- Breastfeed exclusively (give infant only breast milk and no other liquids or solids, not even water, with exception of drops or syrup consisting of vitamins, mineral supplements or medication;
- Breastfeed as often as the child wants, day and night;
- Feed at least 8 to 12 times in 24 hours;
- When away from the child leave expressed breast milk to feed with a cup;
- Avoid using bottles or artificial teats (dummies) as this may interfere with suckling, be difficult to clean and may carry germs that can make your baby sick.

Why is exclusive breastfeeding important?

- Other foods or fluids may damage a young baby's gut and make it easy for infections (including HIV) to get into the baby's body;
- Decreases the risk of diarrhoea;
- It decreases risk of respiratory infections;
- It decreases risk of allergies;

If you have chosen to formula feed your baby, discuss safe preparation and use of formula with the health care worker

Play: Provide ways for your child to see, hear, feel, and move.
Have colorful things to see and reach

Communicate: Look into your child's eyes and smile at him or her
Talk to your child and get a conversation going with sounds or gestures.

HEALTH PROMOTION MESSAGES

6 - 12 months

Feeding:

For all children start complementary foods at 6 months

- Continue breastfeeding;
- Always breastfeed first before giving complementary foods;
- Start giving 2—3 teaspoons of mashed dried beans and/or locally available animal foods daily to supplement the iron in the breastmilk. Examples include egg (yolk), minced meat, fish, chicken/chicken livers, mopani worms. Give soft porridge, vegetables and then fruit;
- Gradually increase the amount and frequency of feeds.
- Children between 6—8 months should have two meals a day. By 12 months this should have increased to 5 small meals per day, whilst frequent breastfeeding continues;
- Offer your baby safe, clean water regularly;
- If the baby is not breastfed, give formula or at least 2 cups of full cream cow's milk (cow's milk can be given from 9 months of age)

Play: Give your child clean household things to handle, bang and drop.

Communicate:

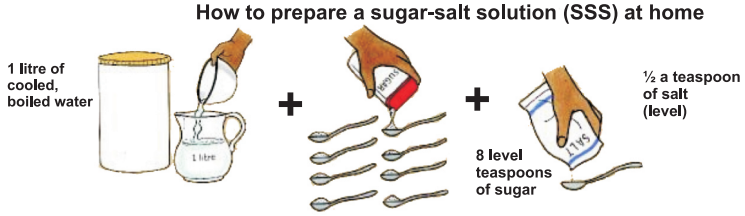
Respond to your child's sounds and interests. Tell your child the names of things and people.

Encourage feeding during illness Suggest an extra meal a day for a week after getting better

Feeding recommendation for DIARRHOEA

- Follow feeding recommendations for the child's age, but give small frequent meals (at least 6 times a day);
- Give a sugar-salt solution (SSS) in addition to feeds. Give SSS after each loose stool, using frequent small sips from a cup (half cup for children under 2 years and 1 cup for children 2—5 years). If the child vomits, wait for 10 minutes then continue, but more slowly

How to prepare a sugar-salt solution (SSS) at home



HEALTH PROMOTION MESSAGES

Feeding: 12 months up to 5 years

- If the child is breastfed, continue breastfeeding as often as the child wants until the child is 2 years and beyond;
- If not breastfeeding, give at least 2 cups of full cream milk, which could be maas, every day;
- Encourage children to eat a variety of foods;
- Feed your children five small meals a day;
- Make starchy foods the basis of a child's main meals;
- Children need plenty of vegetables and fruit every day;
- Children can eat chicken, fish, eggs, beans, soya or peanut butter every day;
- Give foods rich in iron and vitamins A and C;

Iron-rich foods: Liver, kidney, dark green leafy vegetables, egg yolk, dry beans, fortified cereal;
Remember that tea interferes with the absorption of iron. Iron is best absorbed in the presence of vitamin C;
Vitamin A-rich foods: Liver, dark green leafy vegetables, mango, paw paw, yellow sweet potato, full cream milk;
Vitamin C-rich foods: Citrus fruit (oranges, naartjies), guavas, tomatoes;

- If children have sweets, treats or drinks, offer small amounts with meals;
- Offer clean, safe water regularly;
- Encourage children to be active every day.

Play and communicate: 12 months to 2 years

Play: Give your child things to stack up, and to put into containers and take out.

Communicate: Ask your child simple questions. Respond to your child's attempts to talk. Play games like "bye".

Play and communicate: Above 2 years

Play: Help your child count, name, and compare things. Make simple toys for your child.

Communicate: Encourage your child to talk and answer your child's questions. Teach your child stories, songs and games.

DEVELOPMENTAL SCREENING

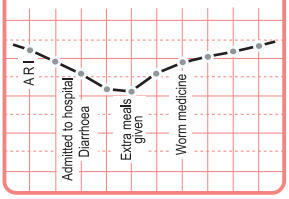
	VISION AND ADAPTIVE	HEARING AND COMMUNICATION	MOTOR DEVELOPMENT
ALWAYS ASK	Can your child see?	Can your child hear and communicate as other children?	Does your child do the the same things as other children of the same age?
14 weeks	Baby follows close objects with eyes	Baby responds to sound by stopping sucking, blinking or turning	Child lifts head when held against shoulder 
6 months	Baby recognises familiar faces	Child turns head to look for sound	Child holds a toy in each hand 
9 months	Child's eyes focus on far objects Eyes move well together (No squint)	Child turns when called	Child sits and plays without support 
18 months	Child looks at small things and pictures	Child points to 3 simple objects Child uses at least 3 words other than names Child understands simple commands	Child walks well  Child uses fingers to feed
3 years	Sees small shapes clearly at 6 metres	Child speaks in simple 3 word sentences	Child runs well and climbs on things
5-6 years: School readiness	No problem with vision, use a Snellen E chart to check	Speaks in full sentences and interact with children and adults	Hops on one foot  Able to draw a stick person
REFER	**Refer the child to the next level of care if child has not achieved the developmental milestone. Refer motor problem to Occupational Therapist/Physiotherapist and hearing and speech problem to Speech therapist/Audiologist if you have the services at your facilities.**		

Girl's Weight-for-Age

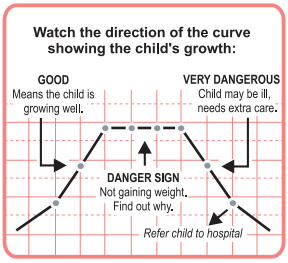
Write on the chart

- Any illness e.g. diarrhoea, ARI, etc.
- Admission to hospital,
- Solids introduced,
- Breastfeeding stopped,
- Birth of next child, etc.

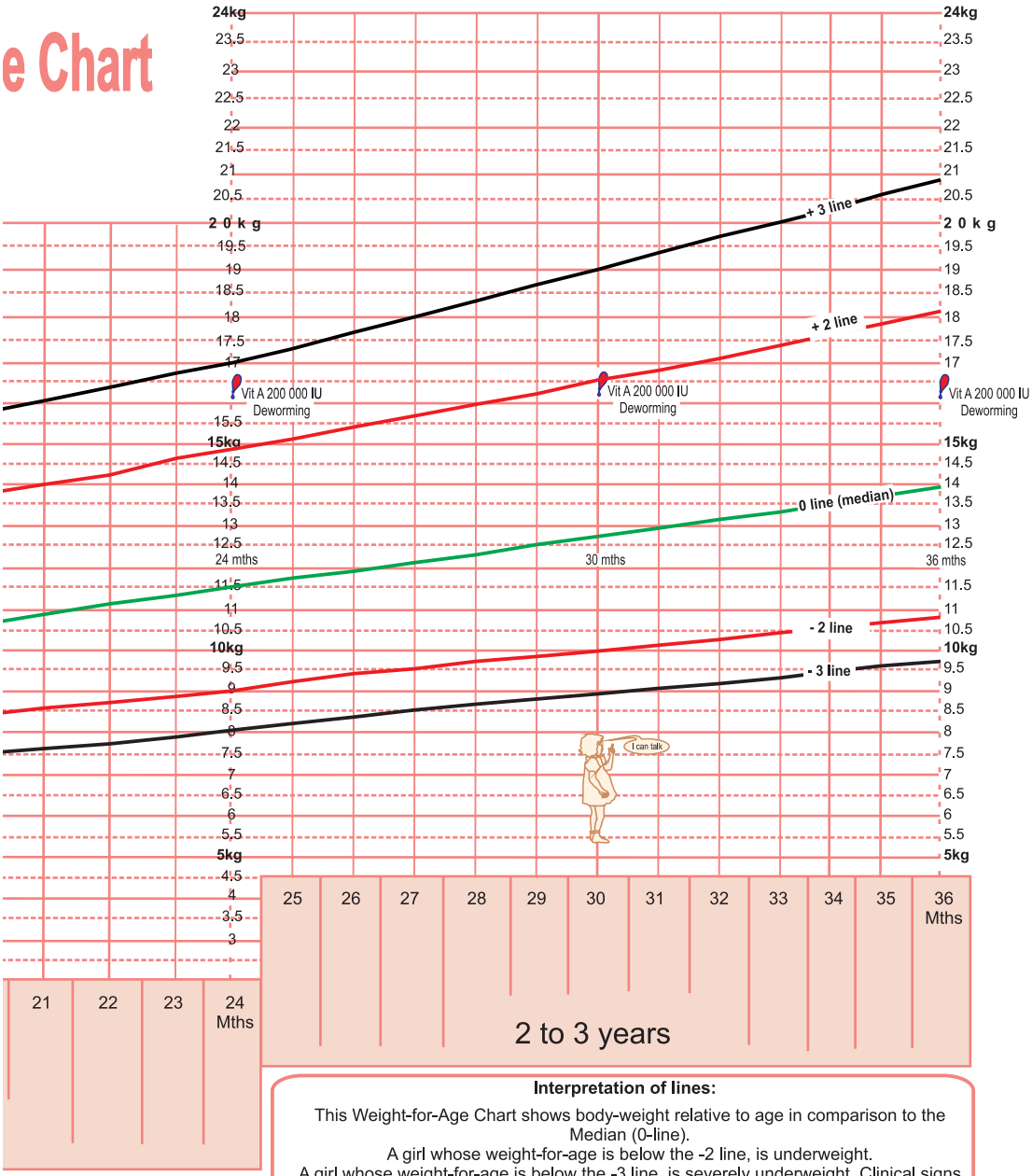
like this:



Watch the direction of the curve showing the child's growth:



e Chart

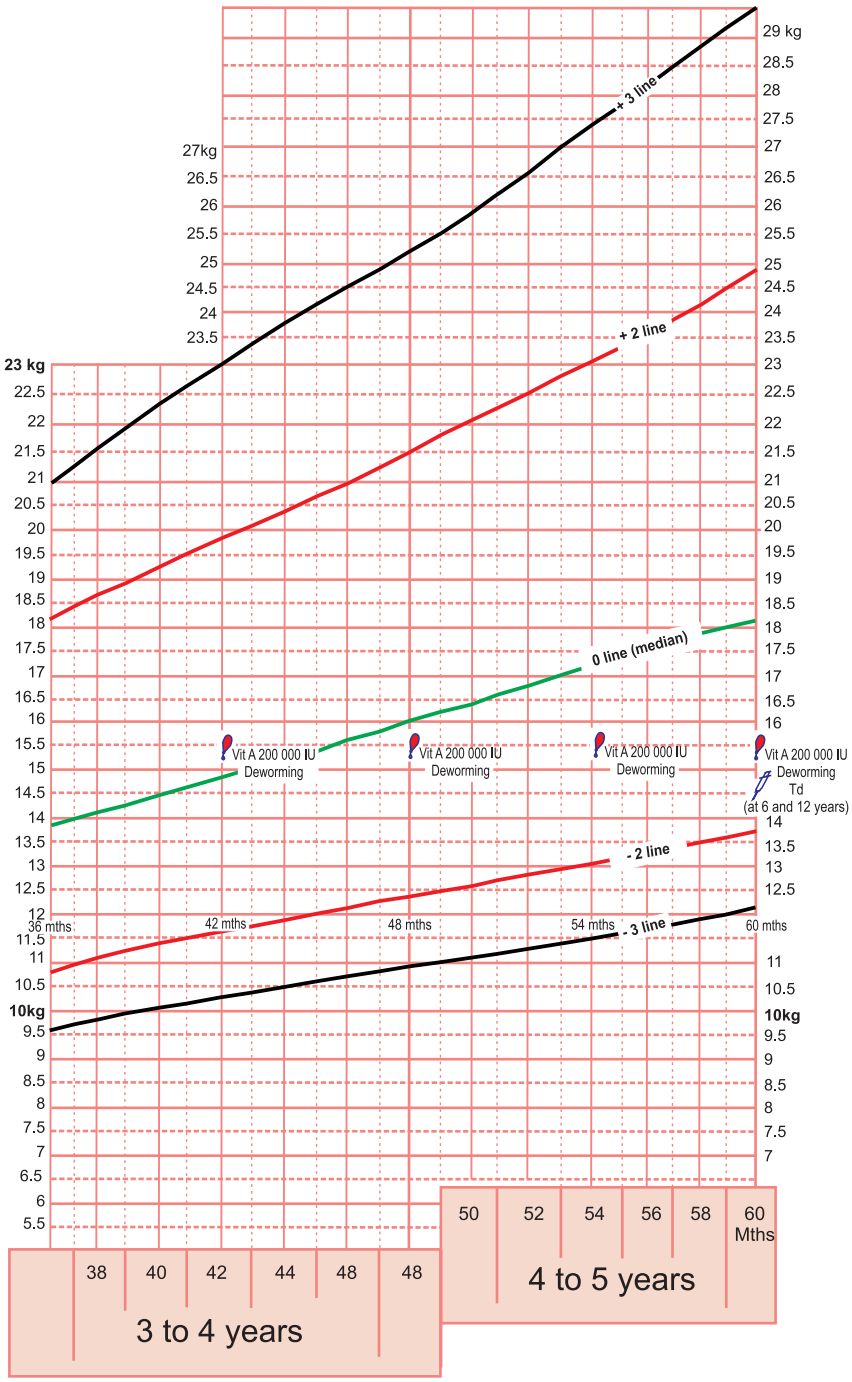


Interpretation of lines:

This Weight-for-Age Chart shows body-weight relative to age in comparison to the Median (0-line).
A girl whose weight-for-age is below the -2 line, is underweight.
A girl whose weight-for-age is below the -3 line, is severely underweight. Clinical signs of Marasmus or Kwashiorkor may be observed.

If her line crosses a z-score line and the shift is away from the median, this may indicate a problem or risk of a problem.

If her line stays close to the median, occasionally crossing above or below it, this is fine.


29 kg
28.5
28
27.5
27kg
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26
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54 mths
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9.5
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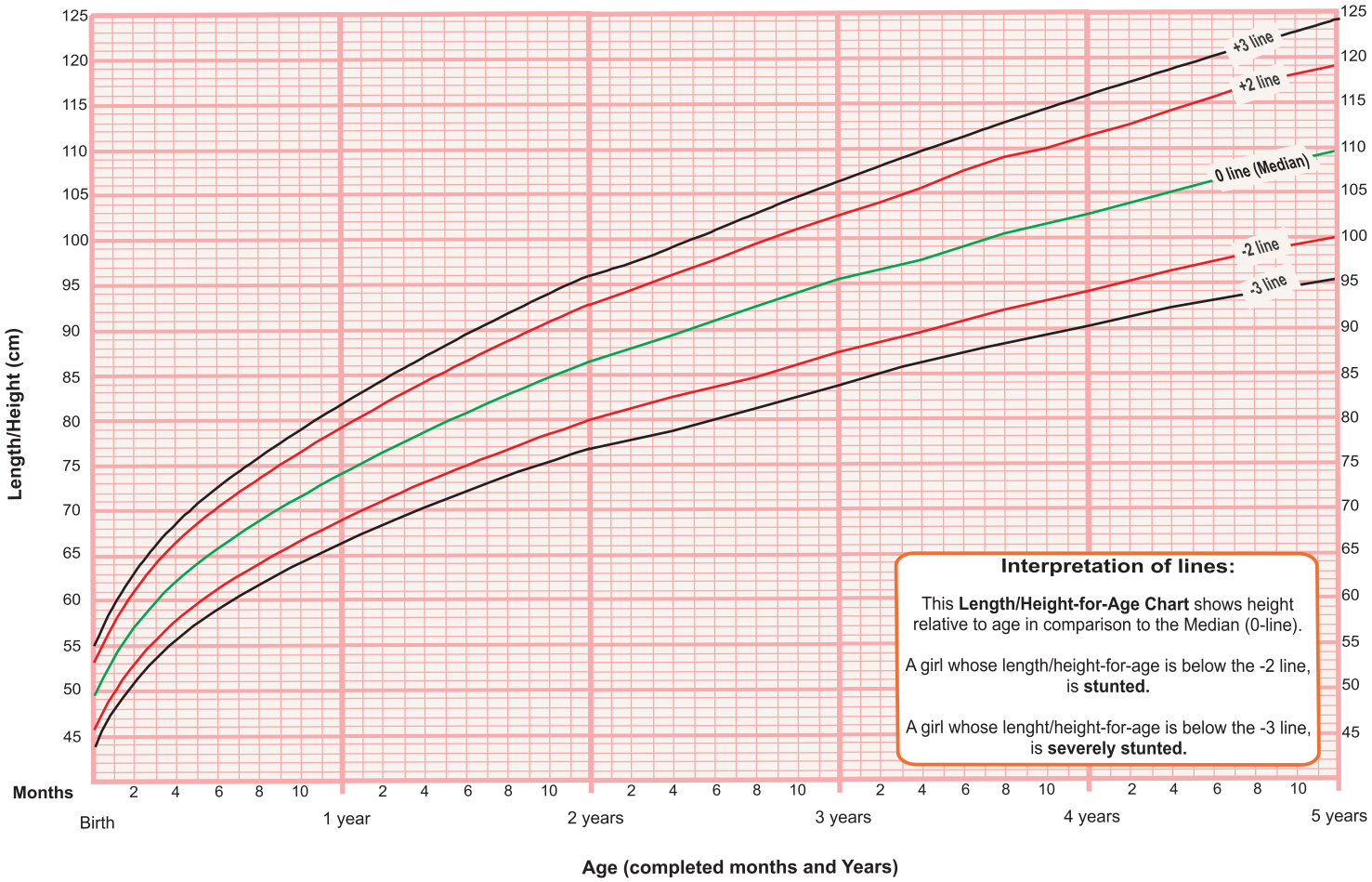
8
8
7.5
7.5
7
7
6.5
6
5.5
+ 3 line
+ 2 line
0 line (median)
- 2 line
- 3 line
Vit A 200 000 IU
Deworming
Vit A 200 000 IU
Deworming
Vit A 200 000 IU
Deworming
Vit A 200 000 IU
Deworming
Td
(at 6 and 12 years)
38
40
42
44
48
48
3 to 4 years
50
52
54
56
58
60
Mths
4 to 5 years

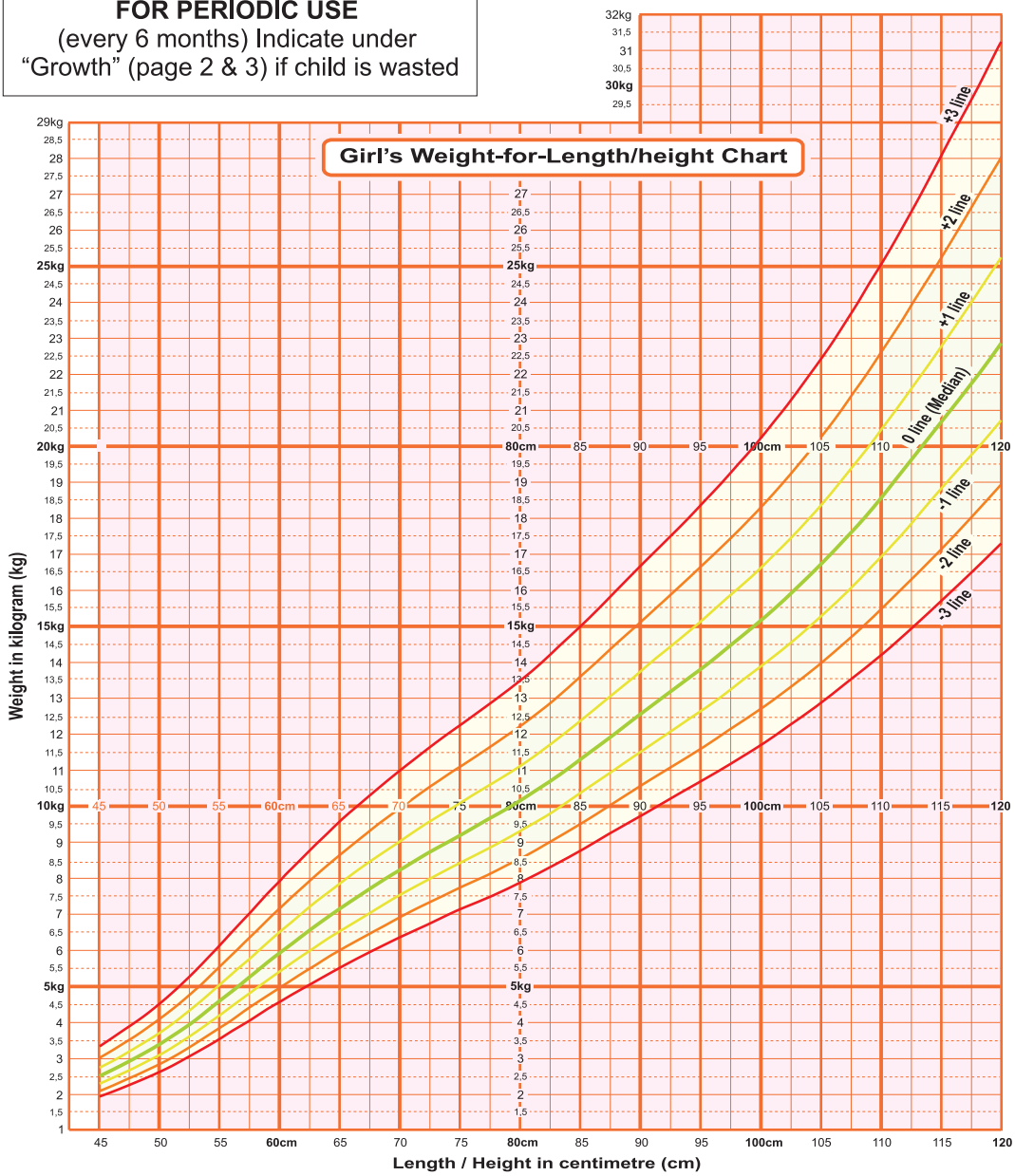
Length/height -for-age GIRLS

Birth to 5 years (z-scores)

FOR PERIODIC USE
(every 6 months) Indicate under "Growth" (page 2 & 3) if child is stunted



FOR PERIODIC USE
(every 6 months) Indicate under
"Growth" (page 2 & 3) if child is wasted



This **Weight-for-Length/height Chart** shows body-weight relative to length/height in comparison to the Median (the 0 z-score line).

A girl whose weight-for-length/height is above the +3 line, is **obese.**

A girl whose weight-for-length/height is above the +2 line, is **overweight.**

A girl whose weight-for-length/height is above the +1 line, shows possible risk of **overweight.**

A girl whose weight-for-length/height is below the -2 line, is **wasted.**

A girl whose weight-for-length/height is below the -3 line, is **severely wasted. Refer for urgent specialised care.**

MID-UPPER ARM CIRCUMFERENCE (MUAC) (Every 3 months)							
Date of visit	**MUAC**	**Date of visit**	**MUAC**	**Date of visit**	**MUAC**	**Date of visit**	**MUAC**

< 11.5 cm indicates severe acute malnutrition (REFER urgently)
≥11.5 < 12.5 cm indicates moderate acute malnutrition (Manage as in IMCI guidelines)

HOSPITAL ADMISSIONS				
Hospital name	Admission number	Date of admission dd/mm/yyyy	Date of discharge dd/mm/yyyy	Discharge diagnosis
		/ /	/ /	
		/ /	/ /	
		/ /	/ /	
		/ /	/ /	
		/ /	/ /	
		/ /	/ /	
		/ /	/ /	
		/ /	/ /	
		/ /	/ /	
		/ /	/ /	
		/ /	/ /	
		/ /	/ /	

NAME OF CLINIC(S) VISITED	
Clinic 1:	Clinic 2:
Clinic 3:	Clinic 4:

ORAL HEALTH EXAMINATIONS

Refer child if scheduled examinations have not been done.
To be completed by Dentist, Dental Therapist or Oral Hygienist.

Schedule of visits:

1st visit on appearance of first tooth

Examiner: _____ Health facility: _____ Date: _____

At age 12 months, when attending immunizations

Examiner: _____ Health facility: _____ Date: _____

In the 2nd year, with other health checks

Examiner: _____ Health facility: _____ Date: _____

In the 3rd year, with other health checks

Examiner: _____ Health facility: _____ Date: _____

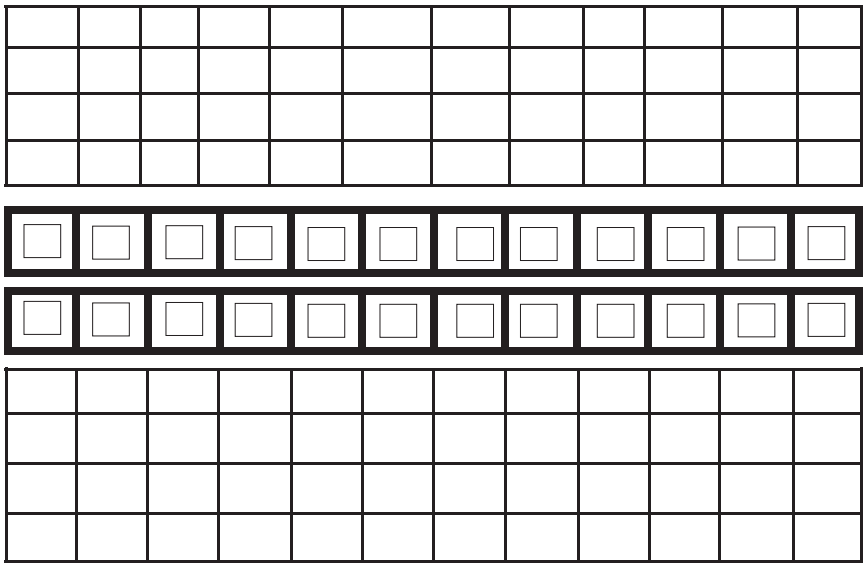
In the 4th year, with other health checks

Examiner: _____ Health facility: _____ Date: _____

In the 5th year, with other health checks

Examiner: _____ Health facility: _____ Date: _____

Use a clean cloth to clean your baby's gums
Use a small soft toothbrush to clean the baby's teeth



CLINICAL NOTES		
Date	Assess and classify	Counsel and treat

CLINICAL NOTES		
Date	Assess and classify	Counsel and treat

CLINICAL NOTES		
Date	Assess and classify	Counsel and treat

CLINICAL NOTES		
Date	**Assess and classify**	**Counsel and treat**

CLINICAL NOTES		
Date	Assess and classify	Counsel and treat

CLINICAL NOTES		
Date	Assess and classify	Counsel and treat

CLINICAL NOTES		
Date	Assess and classify	Counsel and treat

Take your child to the nearest clinic when any of the these danger signs occur:

Vomiting everything

Unable to breastfeed

Child lethargic or unconscious

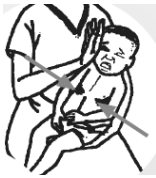
Convulsions

Cough and breathing rate more than 50 breaths per minute

Diarrhoea with sunken eyes or sunken fontanelle

Diarrhoea with blood

Chest indrawing



Child under 2 months and:
- is not feeding
- has fever

Appendix F: Identified risk factors

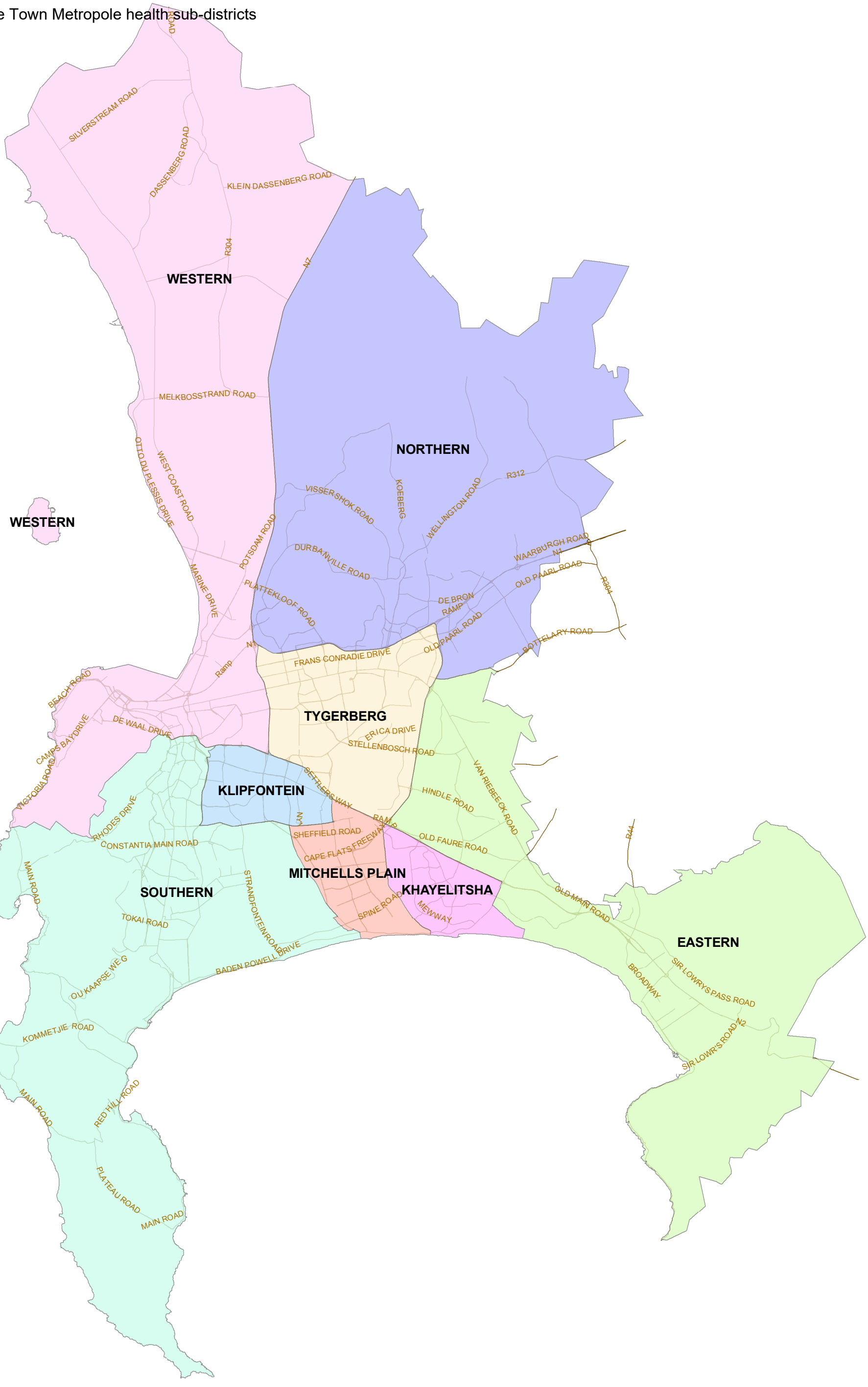
Table 2: Risk factors recorded in the study and the completeness of the variables

Place of birth	**n**	**%**
Clinic	45	15.6%
Home	14	4.9%
Hospital	228	79.2%
Not recorded	1	0.3%
Pregnancy term	**n**	**%**
***Full term**	162	56.3%
***Preterm**	116	40.3%
Not recorded	10	3.5%
Method of delivery	**n**	**%**
C-section	76	26.4%
Normal vaginal	201	69.8%
Not recorded	11	3.8%
Method of feeding	**n**	**%**
Breastfeeding	146	50.7%
Formula	66	22.9%
Both	69	24.0%
None	1	0.3%
Not recorded	6	2.1%
Immunisation up to date	**n**	**%**
Yes	167	58.0%
No	88	30.6%
Not recorded	33	11.5%
Exposed to HIV	**n**	**%**
***Yes**	66	22.9%
No	201	69.8%
Not recorded	21	7.3%
Symptoms	**n**	%
Yes	137	47.6%
No	146	50.7%
Not recorded	5	1.7%
Mattress type	**n**	**%**
Foam rubber	78	27.1%
Inner spring	162	56.3%
Other	9	3.1%
Not recorded	39	13.5%
Co-sleeping	**n**	**%**
***Yes**	264	91.7%
No	14	4.9%
Not recorded	10	3.5%

Number of people in bed	n	%
1	75	26.0%
2	82	28.5%
3	29	10.1%
4	9	3.1%
5	1	0.3%
Not recorded	78	27.1%
Not applicable	14	4.9%
Sleeping position	**n**	**%**
Supine	71	24.7%
Side	128	44.4%
Prone	67	23.3%
Not recorded	22	7.6%
Exposure to 2nd hand tobacco smoke	**n**	**%**
Yes	122	42.4%
No	138	47.9%
Not recorded	28	9.7%
Type of housing	**n**	**%**
Formal	118	41.0%
Informal	93	32.3%
Other	21	7.3%
Not recorded	56	19.4%
Antenatal care	**n**	**%**
Yes	195	67.7%
No	70	24.3%
Not recorded	23	8.0%
Prenatal smoke exposure	**n**	**%**
***Yes**	76	26.4%
No	189	65.6%
Not recorded	23	8.0%
Prenatal alcohol exposure	**n**	**%**
Yes	39	13.5%
No	228	79.2%
Not recorded	21	7.3%

Maternal drug use	n	%
Yes	17	5.9%
No	227	78.8%
Not recorded	44	15.3%
Maternal employment status	**n**	**%**
Employed	70	24.3%
Unemployed	194	67.4%
Not recorded	24	8.3%
Maternal age (at death of infant)	**n**	**%**
<20 years	18	6.3%
20 - 35 years	218	75.7%
<35 years	42	14.6%
Not recorded	10	3.5%
Previous SUDI	n	%
Yes	21	7.3%
No	253	87.8%
Not recorded	14	4.9%
How many previous SUDI?	n	%
1	13	4.5%
2	1	0.3%
Not recorded	7	2.4%
Not applicable	267	92.7%

Appendix G: CApe Town Metropole health sub-districts



Compiled by Strategic Information
Strategic Development Information & GIS
August 2013

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Cape Town: Health Districts

CITY OF CAPE TOWN | ISIXEKO SASEKAPA | STAD KAAPSTAD
THIS CITY WORKS FOR YOU

Appendix H: Search terms

Table 3: The search terms and/or phrases used to search for articles used in the study

Database	Search terms
PubMed	(("infections"[MeSH Terms] OR "infections"[All Fields]) AND sudden[All Fields] AND unexpected[All Fields] AND ("infant death"[MeSH Terms] OR ("infant"[All Fields] AND "death"[All Fields]) OR "infant death"[All Fields])) AND "humans"[MeSH Terms] (prematurity[All Fields] OR preterm[All Fields]) AND (sudden[All Fields] AND unexpected[All Fields] AND ("infant death"[MeSH Terms] OR ("infant"[All Fields] AND "death"[All Fields]) OR "infant death"[All Fields])) Medico-legal[All Fields] AND investigations[All Fields] AND ("south africa"[MeSH Terms] OR ("south"[All Fields] AND "africa"[All Fields]) OR "south africa"[All Fields])
Scopus	(TITLE-ABS-KEY (socioeconomic AND status) AND TITLE-ABS-KEY (sudden AND unexpected AND death AND in AND infancy))