Detection of human rhinovirus in Sudden Unexpected Death in Infancy (SUDI) cases at Tygerberg medico-legal mortuary, Cape Town, South Africa

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Abstract

Background: Infant mortality remains a major global concern. Sudden unexpected death in infancy (SUDI) is common in South Africa, but evidence on the effect of possible risk factors remains limited. Respiratory infections have repeatedly been implicated in the death of these infants, but temporality has not yet been confirmed and SUDI remains a multi-factorial phenomenon.

Methods: This study investigated the relationship between risk factors and positive human rhinovirus in the trachea and lungs of infants admitted to the Tygerberg Medico-legal Mortuary in Cape Town between 2012 and 2019. This study included a total of 407 cases.

Results: The median (range) age of the infants was 9.1 (0.3 to 57.3) weeks. Infants who shared a bed with ≤ 1 person were significantly younger than those where bed-sharing with ≥ 3 people was reported (7.5 vs. 11.9 weeks, p=0.045). Cases with human rhinovirus present in the trachea and lung were significantly older (12.3 and 12.9 weeks, respectively; p<0.001) than those where no human rhinovirus was detected (8.0 and 8.7 weeks). After adjusting for possible confounders, the number of people bed-sharing and human rhinovirus detected in the trachea (standardized β [95%CI], p<0.001 and p=0.016 respectively) were independently associated with age when SUDI occurred.

Conclusion: This study correlated laboratory results with demographic data and risk factors in SUDI cases. The most prominent findings were bed-sharing and the presence of human rhinovirus in the trachea. Infection can be reduced by modifiable means, such as ventilation where possible, sleeping position and providing the infant with a separate sleeping area or bed. However, this may not be possible for many communities in South Africa due to poverty, overcrowding and other socioeconomic reasons.

Keywords: Infection; Human rhinovirus; Sudden unexpected death in infancy; SUDI; Sudden infant death syndrome; SIDS; Cape Town; Western Cape Province; South Africa

Introduction

The history of South Africa is marked with historical colonialism and segregation, which differentiates the nation from other African countries. Analogous to the rest of Africa, nearly half of the population live below the poverty line, and 39% live in overcrowded housing. The country's health inequality is further aggravated by urban-overcrowding, inadequate sanitation, as well as crime and violence, and the effect is poorly understood in infants, where death rate disparities exist between rural and urban infants.[1-5]

Lung Infant mortality is still a major burden to public health globally. The infant mortality rate (IMR) is commonly used as an indicator of population health. According to the World Health Organization (WHO), approximately 2.4 million infant deaths occurred in 2019. Although this was a 50% reduction from 1990, 6 700 neonatal deaths still occurred each day. In 2018, the South African IMR rate was estimated at 29.9 deaths per 1000 live births and previously, Africa had the highest IMR of all WHO regions, i.e., 51 deaths per 1000 live births. This is more than six times higher than the 8 deaths per 1000 live births reported in the WHO European Regions. In 2019, Sub-Saharan Africa recorded the highest neonatal mortality rate of 27 deaths per 1000 live births, translating to 43% of global neonatal deaths (WHO, 2022). A child born in this region was 10 times more likely to die within the first four weeks of life than a child born in a high-income country. However, the reported IMR, especially in low-to-middle-income countries (LMICs), such as Sub-Saharan Africa and South Africa, may be underestimated. Compared to high-income countries, as many LMICs use unreliable measures to capture the appropriate causes of death and estimate infant mortality. Similarly, several infant deaths occurring at home in areas such as Khayelitsha in the Cape Town Metropole, often go unreported for a variety of reasons, e.g., families opting to bury deceased infants on the day of death in the community to avoid mortuary and burial costs.[6-11]

In some instances, infant death is sudden and unexpected, with no clinical signs and symptoms of disease, suggesting the need for medical attention. In South Africa, any unnatural death as defined by the National Health Act (Act 61 of 2003): Regulations Regarding the Rendering of Forensic Pathology Service (R636), including sudden unexpected death in infancy (SUDI) cases, must be subjected to a full medico-legal investigation according

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to the Inquests Act (Act 58 of 1959). SUDI refers to all infants who die suddenly, without an immediately apparent cause, before the age of one year. Once the medico-legal investigation is concluded, the final cause of death is assigned as either

(i) Sudden infant death syndrome (SIDS), where no cause of death could be ascertained despite further investigation

(ii) Other, where the cause of death becomes apparent during the medico-legal investigation, such as infection, aspiration, asphyxia, congenital abnormalities, etc.

(iii) Borderline SIDS, where the medico-legal investigation found suggestive, but insufficient evidence to identify a specific cause of death.[12-17]

Limited data is available on the exact incidence of SIDS in South Africa, but it was reported to be as high as 3.41 per 1 000 live births in Cape Town, which is among the highest globally. Research further shows that SIDS accounts for 50 to 80% of SUDI cases. However, no national or provincial protocol exists for the medico-legal investigation of SUDI in South Africa and each institution follows its own protocols, making comparison between different populations next to impossible. The first publication in the field of infant death describing the investigative practices of SUDI/SIDS in the field of forensic pathology only appeared in 2010. Between January 2012 and December 2016, almost 40% of all infant deaths in two districts in the Western Cape Province were initially unexplained, translating to a SUDI and IMR rate of 7.95 and 20.62 deaths per 1 000 live births, respectively. Respiratory tract infections accounted for more than 70% of these deaths with co-sleeping as the second most common risk factor reported. Despite the observed high prevalence of SUDI/SIDS in Cape Town when compared to the rest of South Africa and the Western Cape, research into SUDI/SIDS is limited. Several South African publications emphasized the need for more comprehensive investigation of SUDI cases provincially and nationally, as the cause of death in approximately 25% of SUDI cases remains unascertained or unknown. Several risk factors for SUDI have been reported in the literature, but no epidemiological or surveillance studies have been done in South Africa to assess the real impact of these risk factors on the burden of disease associated with SUDI. [13,17,18-22]

Commonly reported infant death trends are noted in Cape Town infant studies. Locally, increased frequencies in SUDI cases have been demonstrated during the first three months of life, during the colder months of the year, and in male infants, younger age was significantly associated with infants presenting with infection as a cause of death (p=0.012) prior to adjustment of confounders. In Cape Town several families stay in socioeconomically disadvantaged communities and informal settlements with high population density and overcrowding, jeopardizing infant health and increasing infant mortality. The most common risk factors for SUDI include co-sleeping with the infant, infants sleeping in the prone position, premature birth, parental tobacco smoke exposure or by others living in the same home, caregivers using alcohol and drugs, not adhering to vaccinations schedules, and not seeking medical attention for the infant when noticing symptoms of illness.[16,18,20-24]

The burden of respiratory viral infections in infants is well reported. The contribution of viral pathogens to SUDI cases, however, is less well documented and there is a real need for further research and elucidation of the topic. Respiratory viruses such as respiratory syncytial virus, HRV, human coronavirus, and human adenovirus are commonly detected in infants with respiratory illness, including SUDI cases. When infected, infants commonly present clinically with upper respiratory tract symptoms, such as rhinorrhea, congestion, and cough, but in certain cases, respiratory viral infections, through various pathogenic mechanisms, such as anaphylaxis, can also lead to infant death. Respiratory-related infections are a common cause of infant death in South Africa. Between 2000 and 2004, pneumonia was the most common cause of death in infants in Pretoria (73%) and the second most common in Tygerberg (22%). From 2005 to 2009, it was the most common cause of death at five medico-legal sites across South Africa. One study found infection-related causes of death to be responsible for 66% of SUDI cases, of which 52% were associated with respiratory infections.[14,20,21,25-33]

Publications highlight the importance, sensitivity, and substantiation for the use of molecular viral detection assays. However, decreased post-mortem viral viability, the selection of preferred viral screening-panels and detection assays, and the interpretation and significance of positive viral results are challenging in SUDI cases. Since confirming a cause of death in SUDI cases in South Africa is solely funded by the provincial Departments of Health, the choice and relevance of viral detection panels should be scrutinized and designed to suit diverse infant population groups if it were to be used as part of molecular autopsy protocols.[14,19,21,22]

The general paucity of available data from Cape Town, as well as the greater sub-Saharan African region, necessitated the investigation of sociodemographic factors (age, sex, ethnicity, birth weight, post-mortem interval [PMI], sleeping position and position found, bed-sharing, room ventilation, and type of housing) associated with HRV (A/B/C) present in the trachea and lungs of SUDI cases admitted to Tygerberg Medico-legal Mortuary. Results from the current study significantly contribute to understanding possible risk factors for SUDI in the highly burdened Cape Town area.

Materials and method

Ethics and sample selection

The study was first approved by the Health Research

Ethics Committee (HREC) of Stellenbosch University in 2012 and renewed annually (HREC Registration number: N12/02/007). A waiver of consent was granted by HREC, which allows for collecting and using patient data for additional diagnostic and research purposes without obtaining informed consent from the parents/caregivers. Samples were collected from each SUDI case and subsequently tested with the aim of reporting the results to the Division of Forensic Pathology to assist in the process of determining the cause of death of the infant. Consent was provided by section 3 (a) of the South African Inquests Act (58 of 1959) and Criminal Procedure Acts (1977) whereby samples may be collected from SUDI cases admitted to Tygerberg Medico-legal Mortuary for virological testing to aid in formulating a final cause of death.[15,19]

When the infants are admitted to the Tygerberg Medico-legal Mortuary, information is collected from the parents or caregivers. This includes sex, ethnicity, birth weight (gram), sleeping-position (side, back or other), position found (side, back or other), number of people bed-sharing (≤ 1, 2 or ≥ 3 people), ventilation (no or yes), and housing type (formal or other). This is captured by a Forensic Pathology Officer on a routine questionnaire (form FPS006(b)), utilized by the Western Cape Forensic Pathology Services and the data is made available to the research team for statistical analyses.

Study population and testing for viral infection

Three different one-year studies (n=148, 183 and 161 respectively) that were conducted at the Tygerberg Medico-legal Mortuary between 2012 and 2019 were included in this review. During the post-mortem investigation, flocculated swabs were collected from the trachea and lower lobes of both lungs from these infants and investigated for various viruses with multiplex polymerase chain reaction (PCR) assays. Various extraction kits and PCR viral identification panels were used for the different studies (Table 1). All socio-demographic information from the Forensic Pathology case files was captured on an Excel sheet and included in the statistical analysis.

Table 1: *Sociodemographic information of 407 SUDI cases included in this study.*

Variables		Total population
Age (weeks)		9.1 (0.3 to 57.3)
Birthweight (gram)		2 620 (300 to 4 900)
PMI (days)		4.5 (0 to 19)
Sex	Male	216 (53.1%)
Ethnicity	African	205 (62.3%)
Sleeping position	Stomach	105 (30.9%)
	Side	201 (59.1%)
	Back	33 (9.7%)
	Other[a]	1 (0.3%)
Position found	Stomach	77 (18.9%)
	Side	146 (35.9%)
	Back	68 (16.7%)
	Other[a]	7 (1.7%)
Number of people bed-sharing	≤ 1 person	110 (43.3%)
	2 people	81 (31.9%)
	≥ 3 people	63 (24.8%)
Ventilation[b]	Yes	211 (63.2%)
Housing[c]	Formal	177 (51.5%)
Trachea HRV (A/B/C)	Positive	126 (51.0%)
Lung HRV (A/B/C)	Positive	48 (10.0%)

Note: Data presented as the median (range) or n=(% of cases).

1. Defined as infant sleeping on mother or parent or rolled out of position placed.
2. Defined as an open door or window from the room to the outside.
3. Brick structure that is not a shack, Wendy house, bungalow or flat.

Statistical analysis

All statistical analyses were performed using IBM® SPSS® software (version 25, New York, NY, USA). Data distributions for all the continuous variables were evaluated using Shapiro-Wilk tests, evaluating data histograms and Q-Q plots. Baseline population characteristics were presented as mean ± standard deviation (SD) or median (range: minimum to maximum) for parametric and non-parametric continuous variables, respectively. Categorical variables (sex, ethnicity, seeping position, sleeping position found, season, ventilation in the infant's room, housing type, and HRV detected in lung and trachea samples) were presented as number (n, % of the study population or group). Numerical variables (age, birth weight and PMI) with a skewed distribution were log 10-transformed.

Independent sample t-tests were performed to determine the differences in continuous variable outcomes between groups or population indices. To evaluate the relationship between categorical variable outcomes, Chi-square or Pearson Chi-square tests were performed. Bonferroni post-hoc corrections for multiple comparisons were performed when more than two comparisons were made. Spearman correlations were performed to determine the relationship between continuous variables.

To determine independent associations between independent and dependent variable outcomes, linear regression analyses were performed while adjusting for possible confounding factors. Results were reported as the standardized β coefficient (95% confidence interval [95%CI]) with R, R^2 and adjusted R^2 reported for each analysis. The significant threshold for all statistical analyses was set at $p<0.05$.

Results

Population characteristics

After removing incomplete records from the individual studies, a total of 407 SUDI cases were included in this study. The median (range) age was 9.1 (0.3-57.3) weeks and the birth weight 2 620 g (300-4 900 g). The majority of infants were of African ancestry (62.3%). In exceptional cases, the post-mortem investigation was done on the same day the infant died, mostly due to religious and cultural beliefs of the families. The maximum PMI is often a result of delayed identification of the body at the mortuary, preferential processing of cases which are part of legal proceedings, and where the identification of cause of death can be quickly identified and reported to justice services.

Most infants slept on their sides (59.1%) and infants were also found in this position most frequently. Although there was no clear difference between families that stayed in informal and formal dwellings, most rooms where the infants slept had ventilation. About half of the cases were positive for trachea HRV (A/B/C) and only 10% were positive for lung HRV (A/B/C) (Table 1).

Relationship between SUDI risk factors and HRV results

Age of death was significantly higher in infants that reported bed-sharing with ≥ 3 people compared to ≤ 1 person (p=0.045). It was also significantly higher for positive trachea and lung HRV (A/B/C) infection compared to their naïve counterparts, respectively (p=0.001 and p<0.001). In a separate analysis, no significant correlation was observed between age of death and birth weight (Spearman's rho=0.050, p=0.346, n=352). No other significant associations between age of death and other variable outcomes were observed.

Positive HRV (A/B/C) results in the trachea were significantly associated with number of people bed-sharing and ventilation in the infant's room (p=0.001 and p<0.001, respectively). Similarly, positive HRV (A/B/C) results in the lung were also significantly associated with number of people bed-sharing and ventilation (p=0.001 and p<0.001, respectively). A dependent relationship (p<0.005) between positive HRV (A/B/C) results in the trachea and lungs was further observed (Table 2).

Table 2: *Sociodemographic information of 407 SUDI cases with positive HRV (A/B/C) results in the trachea and lungs.*

Variable		Age of infant (weeks)	Trachea HRV positive	Lung HRV positive
Sex	Male	8.9 (0.7 to 56.1)	65 (51.6%)	47 (56.0%)
	Female	9.9 (0.3 to 57.3)	61 (48.4%)	37 (44.0%)
Ethnicity	African	9.0 (0.6 to 57.3)	33 (57.9%)	18 (50.0%)
	Mixed	9.1 (0.3 to 49.4)	34 (42.1%)	18 (50.0%)
Sleeping position	Stomach	9.0 (1.4 to 49.4)	29 (29.6%)	16 (27.1%)
	Side	8.3 (0.7 to 57.3)	61 (62.2%)	35 (59.3%)
	Back	12.9 (0.4 to 50.4)	8 (8.2%)	8 (13.6%)
	Other	-	0 (0%)	0 (0%)
Position found	Stomach	9.0 (1.4 to 25.6)	20 (28.2%)	12 (26.7%)
	Side	8.0 (0.7 to 42.6)	30 (42.3%)	18 (40.0%)
	Back	11.0 (0.4 to 56.1)	19 (26.8%)	114 (31.1%)
	Other	11.3 (2.4 to 37.7)	2 (2.8%)	1 (2.2%)
Number of people bed-sharing	≤ 1 person	7.5 (0.4 to 52.0)*	24 (29.6%)**	10 (22.7%)
	2 people	9.3 (1.1 to 50.9)	22 (27.2%)	12 (27.3%)
	≥ 3 people	11.9 (0.7 to 49.6)	35 (43.2%)	22 (50.0%)**
Ventilation in infant's room	No	9.4 (1.0 to 49.6)	49 (51.6%)**	30 (56.6%)**
	Yes	9.2 (0.4 to 57.3)	46 (48.4%)	23 (43.4%)
Housing	Formal	9.9 (0.4 to 56.1)	45 (50.0%)	24 (44.4%)
	Other	9.1 (0.6 to 57.3)	45 (50.0%)	26 (55.6%)
Trachea HRV (A/B/C)	No	8.0 (0.3 to 57.3)**	-	8 (11.9%)**
	Yes	12.3 (1.0 to 52.0)	-	59 (88.1%)
Lung HRV (A/B/C)	No	8.7 (0.3 to 57.3)**	-	-
	Yes	12.9 (1.3 to 52.0)	-	-

Note: Data presented as the median (range) or n=(% of cases). *, p<0.05; **, p<0.01.

Regressions

Following linear regression analyses, the number of people bed-sharing (0.385 [0.176 to 0.593], p<0.001) and positive HRV (A/B/C) results in the trachea (0.286 [0.056 to 0.516], p=0.016) were positively associated with the age of death (Table 3).

Table 3: *Linear regression results showing independent predictors of age of death.*

Predictor	Standardised β	95% CI Lower	95% CI Upper	p-value
Sex (female)	-0.031	-0.24	0.178	0.77

Ethnicity (mixed)	-0.125	-0.342	0.091	0.252
Birth weight (g)	-0.098	-0.352	0.157	0.447
Sleeping position (back)	-0.07	-0.3	0.159	0.543
Position found (back)	0.124	-0.103	0.35	0.28
Number of people bed-sharing	0.385	0.176	0.593	<0.001
Ventilation (yes)	0.259	-0.012	0.53	0.061
Housing type (informal)	-0.023	-0.252	0.205	0.84
Trachea HRV A/B/C (positive)	0.286	0.056	0.516	0.016
Lung HRV A/B/C (positive)	0.007	-0.265	0.278	0.961

Note: $R=0.546$, $R^2=0.298$, Adjusted $R^2=0.181$. (n=78).

Discussion

Risk factors associated with infant death and SUDI are well-defined in the literature, including but not limited to age, bed-sharing, infant sleeping position, socioeconomic level, and the presence of infection. The pathogenesis of these risk factors remains to be elucidated.[16,21,34]

Globally, SUDI occurs most frequently between the ages of 2 to 4 months. This trend was also noted in South Africa, the Western Cape Province, Cape Town, and this study that was conducted in the East Metropole of Cape Town. Infants may be more vulnerable to death at this age due to genetic factors, rapid organ development, microbiota diversity attributed to mode of parturition, and exposure to pathogens and irritants. The risk profile of SUDI cases confirms a culmination of complex interplay between modifiable and modifiable factors and research therefore requires a multidisciplinary approach. None of the risk factors have been confirmed to be the sole cause of death, as these infants are regularly and consistently exposed to more than one risk factor at a time. However, the profiling of a SUDI risk assessment protocol may propel the development of a specific risk factor screening tool for SUDI.[13,19-22,35-43]

Respiratory viruses are commonly detected in SUDI cases and viral infections specifically burden infants and children under the age of five globally. South African studies report a high incidence of respiratory-related deaths in SUDI populations, but have not highlighted key viruses or the possible pathophysiology leading to SUDI. HRV infection occurs through inhalation of aerosolized droplets or physical inoculation following contact with fomites. Return-to-school is implicated in HRV transmission rates in children who experience multiple infections per year. In this study, HRV was detected five times more common in the trachea than lungs of the cases. After adjusting for confounders infants with HRV present in the trachea were significantly older than those without infection. However, these post-mortem molecular findings cannot entirely infer death due to infection. Some micro-organisms propagate during putrefaction and played no role in death. With the exception of only a few viruses, specific viruses cannot be confirmed on lung morphology alone.[8,16,17,21,35,44-53]

Airway occlusion during viral infection in infants is caused by immune or viral mechanisms and can lead to death. The respiratory mucosal layers are covered by mucus, a viscoelastic gel with a mucin glycoprotein framework that provides physical protection against viral entry and contributes to the innate defense system. It traps and expels pathogens and debris via muco-ciliary clearance, essentially preventing the spread of infection to the lower airways. Respiratory viruses such as HRV induce mucin production leading to increased mucus production, but the protection provided by mucin production and -secretion seems to be lost when hyper-secreted in response to infection, leading to airway obstruction. HRV is synonymous with rhinorrhea and nasal obstruction which is associated with mucus hypersecretion and is known to cause upper airway obstructive diseases such as croup. Infants have a narrow nasopharynx and short trachea compared to adults. Immature respiratory muscles cannot compensate for airflow obstruction. This can be aggravated by enlarging tonsils from 12 weeks of age. Additionally, the tongue can also more easily obstructs the airway due to its size. As a result, the structural integrity of the infant airway is susceptible to dynamic airway collapse.[54-62]

Older infants with HRV infection in the trachea in this study could possibly be a result of an inverse relationship between maternally derived passive immunity and infant age. Maternal IgG antibodies start to wane at age two to four months. The decline in immunity often leads to viral infection, which could be fatal in older infants. The distribution of HRV subtypes varies per age group with HRV-A more frequently affecting adult populations, while HRV-C is more common in older infants, although it is unclear whether this leads to more severe disease. Despite the infection risk, infants are innately at the highest risk of SUDI at two to four months of age when organ systems are rapidly developing, rendering the infant vulnerable to disease, and possibly death.[14,21,38,45,63-68]

HRV primarily replicates in and infects the epithelial cells in the upper and lower respiratory tracts. All three species of HRV (A, B and C) circulate in South Africa and may be the most common viral infection in young South African children, as demonstrated in children presenting with acute wheezing at Red Cross War Memorial Children's Hospital in Cape Town, where HRV was the most common viral infection in young African children. Progression from upper to lower respiratory tract infection may be dependent on the intrinsic virulence of the virus, age of the patient, underlying illness, or underlying immunodeficiency. The optimal temperature for HRV replication is 33 to 35°C, while the lung has an average temperature of 37°C. The cooler temperature of the lower respiratory tract therefore provides a favorable environment for HRV replication.[68-73]

Bed-sharing is a known risk factor for SUDI, especially in infants under the age of 8-11 weeks. Such infants are at risk of experiencing declined oxygen saturation, periodic breathing, and partial airway obstruction by bedding, overheating, accidental suffocation and strangulation in bed by overlaying and wedging. It also facilitates shifting into a face-down or prone sleeping position, which presents its own risks. This is the first study to report the number of individuals bed-sharing with an infant in SUDI cases in South Africa. The results showed that infants who bed-shared with more individuals were significantly older than those who shared with fewer individuals even after adjusting for confounding factors. This could be attributed to the perceived positive effects of bed-sharing, such as mother-to-infant bodily contact, promoting beneficial behavioral and physiological changes in the infant, and increased milk supply due to a higher frequency of night-time breastfeeding. Additionally, the mother may immediately notice signs of clinical distress in the infant. Bed-sharing tends to be more common when infants are younger, as this may facilitate breastfeeding, among other reasons. While some studies failed to find additional associated risks in SUDI, there is a myriad of literature to support the opposite. The practice of bed-sharing is more prevalent in non-Western cultures, such as Africa than in China and The United States of America.[74-90]

The apparent correlation found in this study between SUDI and African ancestry has not been investigated and could be purely co-incidental. SUDI also occurs in high-income areas, but those cases will not necessarily be investigated at the academic Tygerberg Medico-legal Mortuary. In the absence of genetic and other specialized investigations, the most plausible explanation is that during this study period, the majority of infants admitted for investigation at the Tygerberg Medico-legal Mortuary were of African descent, with very few from other ethnic groups. The racial profile from this study does therefore not represent SUDI in South Africa and should be interpreted in parallel with the demographic profile of the referral area of the Tygerberg Medico-legal Mortuary. Between 2001 and 2011, this area's population nearly doubled and ranked the second-highest populated area in Cape Town (City of Cape Town, 2019). The 2011 Census of the City of Cape Town showed almost a one-third increase in population number from 2001 to 2011, of which the majority were Colored (64%), followed by Black African (19%) and Caucasian (4%). However, in children under the age of four, the majority were African (11%) and only 4% were Caucasian (Strategic Development Information and Geographic Information Systems, City of Cape Town, 2013).

In the Tygerberg District, less than 25% of the residents lived in informal housing, mostly in Bonteheuwel, Bishop Lavis, and a part of Belhar. These neighborhoods are characterized by lower-than-average household income and individuals are therefore more vulnerable to stresses and shocks. In South Africa, formal dwellings are defined as homes that are built according to approved building plans and include standalone houses, flats or apartments, and townhouses. Conversely, informal dwellings include makeshift structures without approved architectural plans, such as shacks, which are built with iron, wood, or other non-durable materials. This study found an equal distribution of cases from formal and informal settlements. According to the 2011 Census, the majority of Africans in the referral area of the Tygerberg Medico-legal Mortuary lived in informal dwellings. These housing conditions may expose an infant to risks associated with increased susceptibility to infection, morbidity and mortality (Sopeyin et al, 2020), especially inadequate ventilation and biomass fuels used for lighting, cooking and heating. One could postulate that the higher incidence of African infants is merely a reflection of the population demographics of the referral area, but until such time the Stats SA Census 2022 provides refreshed demographic data, it is impossible to infer a relationship between ethnicity and SUDI.[13,40,41,91-94]

Ventilation serves to dilute and remove indoor pollutants. Natural ventilation comprises indoor air which is replaced with air from the outdoors through windows and openings, while mechanical ventilation includes the use of energy-requiring machinery, such as fans. Natural ventilation is low maintenance and regarded as an acceptable means of preventing infection and the spread of pandemics in LMICs. This may also decrease transmission of airborne pathogens more effectively than mechanical ventilation. However, outside air quality, especially in high pollution areas, is affected by pollutants containing copper, iron, nickel and other metals, which may be introduced into a room and contribute to household air pollution. Optimal natural ventilation is generally impaired in informal homes in Africa. Although most infants in our study reportedly slept in rooms with natural ventilation, significantly more infants presented with HRV infection of the trachea and lung than those without ventilation. Even reduced natural ventilation increases the risk of airborne pathogen transmission and affects airborne viral load and respiratory tract infections in children. This is evident by damage in the respiratory tracts and subsequent opportunistic viral infection as a result of increased exposure to household pollution. South Africa has one of the highest global indoor air pollution mortality rates per million populations, aggravated by certain cooking methods, personal care products, and tobacco smoke exposure, resulting in respiratory-related death and associations with respiratory infections, such as pneumonia and tuberculosis. The effect of tobacco smoke exposure on pediatric airways starts with airway thickening, followed by upregulated mucus production, immune dysfunction, and inflammation, leaving the compromised airways more susceptible to respiratory viral infections. The lack of ventilation and the effect of air pollution and molecular aging and cardiovascular risk have been described in healthy women in Cape Town and may be extrapolated to infants.[40,41,94-100]

In keeping with other reports, our study also found more male than female infants succumbing to SUDI. The exact contribution of sex to SUDI is still not clearly defined, but can be attributed to genetic and biological characteristics of the male sex, which renders male infants more susceptible to disease, premature death, and overall mortality.

Side and prone sleeping positions have been associated with infant death and were also evident in this study. Both Medico-legal Mortuaries in Cape Town still report this tendency in more than 80% of their SUDI populations, despite awareness campaigns and interventions for safe sleeping practices in South Africa. Intentionally placing in the prone position to sleep is influenced by medical advice, the parent's own opinion on sleep practices or the opinions of other family members. Infant death associated with sleeping position may be a result of hypercapnia followed by subsequent hypoxia due to rebreathing exhaled carbon dioxide, sub-optimal respiration, as the infant's weight is placed on the abdomen and rib-cage, and thermal stress due to lack of heat loss. If infants have mild respiratory symptoms, the subsequent increase in nasal temperature may catalyze bacterial growth and increase the density of bacterial colonization are combined, the risk of SUDI more than doubles. However, the data pertaining to sleeping position found at death scenes need to be interpreted with caution. The process of rigor mortis may alter the infant's original position, recall bias from the family may influence the data provided during the interview process, or bed-sharing individuals may have moved the infant's body before noticing death.[101-111]

A routine interview is conducted with the parents or caregivers of all SUDI cases admitted to Tygerberg Medico-legal Mortuary to collect socio-demographic and other information on the infant. A major limitation of the data collection process had to rely on the information that families provide, which is subject to recall and interviewer bias, amongst others. It must also be noted that in many cases, the family or caregivers have limited education and understanding, and questions may be interpreted differently by different individuals. Therefore, the information provided in the interview process regarding the circumstances around and leading to the infant's death can often not be verified.

Conclusion

This is the first study investigating socio-demographic factors associated with respiratory viral infections in SUDI cases at Tygerberg Medico-legal Mortuary. Although molecular testing has limited value in post-mortem cases due to decreased viral viability, when used with other factors, the role of infection in these cases can be described. The detection of specific viruses in combination with demographic data should facilitate the development and initiation of targeted interventions in resource-strapped communities. Infection can be reduced by modifiable means, such as ventilation where possible, sleeping position and providing the infant with a separate sleeping area or bed. However, this may not be possible for many communities in South Africa due to poverty, overcrowding and other socioeconomic reasons. Institutions should therefore engage in multidisciplinary research to properly define and implement national guidelines and protocols to equip all role players on focusing on preventative strategies according to the risk factors to limit unexplained infant deaths. This will not be possible without proper financial support from both public and private sectors.

Credit author statement

Conceptualization, Data curation; Formal analysis; Funding acquisition, Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing – Original Draft; Writing Review and Editing

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Institutional board review statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Stellenbosch University (protocol code N12/02/07; date of first registration 07/03/2012; date of latest renewal 21/10/2021).

Informed consent statement

All unnatural deaths, including SUDI, fall under the auspices of the South African Inquests Act (Act 58 of 1959) and Criminal Procedures Act (Act 51 of 1977) and a full medico-legal investigation must be performed to ascertain the cause of death. The Health Research Ethics Committee of Stellenbosch University granted a waiver of consent, as there was no deviation from the institutional investigation protocol for SUDI cases, and consent was provided for by section 3(a) of the Inquests Act (Act 58 of 1959) and was statutory.

Research Article

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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