Research Article

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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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%)
	Stomach	9.0 (1.4 to 49.4)	29 (29.6%)	16 (27.1%)
Sleeping position	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		p-value
		Lower	Upper	
Sex (female)	-0.031	-0.24	0.178	0.77

sure, 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.

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