LOWER RESPIRATORY TRACT INFECTION IN SUDDEN UNEXPECTED INFANT DEATHS

by

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A dissertation submitted in
partial fulfilment of the requirements for the degree of
M Phil Paediatric Pathology

DIVISION OF ANATOMICAL PATHOLOGY

UNIVERSITY OF CAPE TOWN

2012

ACKNOWLEDGMENTS

This dissertation was done under the supervision of

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University of Cape Town.

I am indebted to them for their guidance and support.

I would also like to acknowledge Professor LJ Martin from the Department Forensic Medicine and Toxicology, Faculty of Health Sciences, University of Cape Town for her patience and understanding.

I would also like to thank and acknowledge: Mrs J Mehl, Mrs C Beukes, Senior Forensic Officer S Benjamin, Forensic officer Delport, for their assistance and support and Mrs M. Kellet for assisting with typing of this manuscript.

ABSTRACT

Pneumonia due to polymicrobial infection is known to increase the severity and risk of fatality among young children. A retrospective study was undertaken on Sudden Unexpected Infant Death cases occurring, between 1 May and 30 September 2009, which were admitted to a medico-legal mortuary servicing the Cape Town western metropole.

Published studies have shown the risk factors for lower respiratory tract infection to include lack of breast feeding, prenatal and environmental tobacco smoke exposure, prematurity, immunosuppression, underlying medical conditions and overcrowding. The present study was aimed at determining which of the known epidemiological factors were associated with SUDI death types admitted to this mortuary and to describe the associated histopathology. In addition, in the knowledge that drugs, specifically Methamphetamine are widely used on the Cape Flats from where almost all this mortuary's SUDI cases are derived, this study has attempted to find out whether or not the usage of drugs by the caregiver at the time of infant death was another independent risk factor in SUDI deaths.

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GLOSSARY OF TERMS AND ABBREVIATIONS

SUDI	Sudden Unexpected death in Infancy
SIDS	Sudden infant death Syndrome
RSV	Respiratory Syncytial Virus
CMV	Cytomegalovirus
SRFPL	Salt River Forensic Pathology Laboratory
CESDI	Confidential enquiries into Stillbirths and Deaths in Infancy
PCR	Polymerase Chain Reaction
HSV	Herpes Simplex Virus
vLRTI	Viral lower respiratory tract infection
mLRTI	Mixed/Polymicrobial (bacterial and viral) lower respiratory tract infection
URTI	Upper respiratory tract infection
CSF	Cerebrospinal fluid
UCT	University of Cape Town
Lack BF	Lack of breast feeding
PrenSE	Prenatal smoke exposure
Env SE	Environmental smoke exposure
Immunosup	Immunosuppression
Medical dx	Medical disease
Prem	Prematurity
IAH	Intra-alveolar haemorrhage
ASP	Aspiration of gastric content
v myocarditis	Viral type myocarditis

AIM AND METHODOLOGY

It is known that lower respiratory tract infection occurs predominantly in rainy seasons. In Cape Town these seasons include May to September. In an attempt to ascertain the relationship between sudden unexpected infant death and lower respiratory tract infection the study aims were as follows:

AIMS

1. To determine the cause of death in cases of sudden unexpected infant death admitted to the SRM between 1 May and 30 September 2009.

2. To determine the proportion of deaths due to lower respiratory tract infection, the proportion caused by polymicrobial organisms and the proportion caused by single pathogens.

3. To describe the histopathology associated with sudden infant death due to lower respiratory tract infection.

4. To identify the risk factors associated with sudden infant death in cases with lower respiratory tract infection admitted to the SRFPL in this period namely:

    - Prematurity
    - Immunosuppression
    - Maternal smoking
    - Environmental tobacco smoke exposure
    - Absence of breast feeding
    - Low socio-economic status
    - Overcrowding
    - Underlying medical conditions (chronic lung disease, congenital heart disease, trisomy 21)

5. To determine the gender, race, and age of the deceased infant.

6. To determine the proportion of cases where caregivers used alcohol and drugs on the day of death and its amount.

METHODOLOGY

Study design

The study is a descriptive study, the data having been obtained from the SRFPL in Cape Town.

Study population

The study population consisted of all infants aged 7 to 365 days admitted to the Salt River Forensic Pathology Laboratory in Cape Town, between 1 May and 30 September 2009 who had died suddenly and unexpectedly in apparent natural circumstances. Foetuses and infants under 7 days were deliberately excluded from the study as the spectrum of causation of death (involving mainly congenital abnormalities, diseases of prematurity and of the placenta and cord) is different to that in the older infant. Furthermore, for the purposes of this study, lower respiratory tract infection and its mode of presentation, was expected to be more prevalent in the older infant. The criteria used for selection were as follows:

1. The infants demonstrated no symptoms of disease before death
2. Infants who were reported to have had minor symptoms by caregivers, and death was unexpected.

Logistics

Before the study was undertaken, a standardised SUDI (Sudden Unexpected Death in Infancy) questionnaire was devised for use at the Salt River Forensic Pathology Laboratory, to capture data regarding sudden unexpected infant death cases admitted to the facility.

Application was made to procure the necessary equipment required for the study from National Health Laboratory Service.

The proposal for the dissertation was submitted to UCT Ethics Committee and this was approved in November 2010.

Confidentiality regarding the identity was maintained. All cases including the study cases, admitted to the facility are medico-legal/forensic cases and thus information regarding them is subjudice. All cases are assigned a mortuary and an inquest case number. No

personal detail was used when the data was captured. Photography of all cases admitted to the facility is a standard operational procedure and was thus adhered to. The mortuary files are kept at the facility and the autopsy data regarding the death cases are kept at the Division of Forensic Medicine and Toxicology, UCT, Cape Town and are thus in safe keeping.

Data Management and Analysis

1. The data for risk factors were extracted from the standardized SUDI questionnaire currently in use at the SRFPL, when infants have died sudden and unexpectedly after being put to sleep. This is attached to the protocol.

2. The cause for death was determined by reviewing the autopsy findings. The autopsies were conducted by standardized protocol, which included external and internal examination of the infant's body, assessment of nutritional status and an X-ray examination of the entire body, so as to exclude bone fractures or skeletal abnormalities.

3. Special investigations performed in order to determine cause of death included:

    a. Histology on the tissue sections retained during the autopsy for microscopy. The tissues sampled included:

        - A section of each lung lobe, so as to determine the presence or absence, and extent of lower respiratory tract infection, gastric content aspiration and intra-alveolar haemorrhage. Where a mixed/polymicrobial infection was found to be present, a Gram stain was done so as to demonstrate bacteria.
        - A section of the thymus, so as to ascertain stress reaction.
        - A section of the larynx so as to ascertain the presence or absence of URTI
        - A section of the heart so as ascertain the presence or absence of myocarditis
        - Six brain sections so as to determine the presence or absence of meningitis and encephalitis. These included a section of the cortex, the pons, the midbrain, the left and the right hippocampus, a thalamus and associated ventricle.
        - Routine sections of the kidneys, gut, liver and spleen.

    No reserve tissue was kept. Tissues sampled were placed directly into cassettes at the mortuary, which were then processed and embedded in paraffin blocks.

    For comparison, lung slides of 3 sudden but accident-related child death cases were used as controls. These were not age matched controls. The number of lung sections per case examined was 4 to 5.

b. Bacteriological cultures were performed on samples of CSF and blood, and swabs of the lower trachea and main bronchi.

c. Virology PCR studies were performed on lung samples

d. A drug screens were performed on a blood samples using liquid gas chromatography and mass spectrometry.

The data was collated and analysed using Micro Soft Excel 2010.

Chapter 1

INTRODUCTION

Pneumonia is the most important, foremost cause of death in children under 5 years of age. In 2000, at the United Nations Millenium Summit, delegates from the United Nations member states reached a consensus to decrease the mortality rate in children under 5 years by 60% by 2015. In order to achieve this goal, given the global impact pneumonia has on child mortality, it was recognised that a significant reduction in deaths due to this disease needs to be accomplished.

Research into pneumonia has increased since 2007 when people became aware of the significant role it played in child mortality, however very little research has been directed at elucidating its association with sudden unexpected death in infancy.

Chapter 2

LITERATURE REVIEW ON CHILDHOOD LOWER RESPIRATORY TRACT INFECTION AND SUDDEN DEATH IN INFANCY.

INTRODUCTION

Lower respiratory tract infection which encompasses bronchiolitis, pneumonia and bronchopneumonia is the most important killer disease in children under 5 years of age accounting for approximately 20% of all childhood fatalities [(1)]. Globally, this disease causes 156 million fatalities yearly of which 151 million occur in developing countries[(2)]. It is also one of the most important causes of hospital admissions in poor and developing countries[(3)].

AETIOLOGY OF LOWER RESPIRATORY TRACT INFECTION

Pneumonia in children is also associated with chronic respiratory disease [(4)]. In Africa pneumonia is the leading cause of death in children under 5 years of age accounting for 20% of all fatalities in this age group [(5)]. HIV Type I infection has compounded the world wide encumbrance of lower respiratory tract infection. It increases the severity and mortality of pneumonia. Although bacterial pathogens are known to the predominant cause of pneumonia fatalities in those infected with HIV infection, the pathogen spectrum is broader encompassing gram-negative infections and *Pneumocystsis jiroveci* [(6)]. In South African children the latter is considered to be a significant "AIDS defining" infection [(7)] and causes 1 in 4 pneumonia deaths in infants. [(8)]. Furthermore in areas where M. tuberculosis is rife, this pathogen is considered to be an important cause of acute pneumonia [(6)]. Coovadia et al considers HIV in infancy to increase the risk of developing Tuberculosis [(9)]. Tuberculosis has been found to occur frequently in both HIV infected and HIV uninfected children. CMV is one of the viruses which with M. Tuberculosis and P. jirovecii cause opportunistic infection in HIV infected children [(8)].

Community acquired pneumonia manifests differently in adults and children. In childhood its incidence peaks in those under 5 years of age whereas in the adult population the incidence peaks in those 75 years and older [(10)].

In developing countries S. pneumoniae and H. influenzae have been identified as the main bacterial pathogens causing childhood pneumonia. The incidence in Africa of H-influenzae type b has however decreased since Hib immunization has been initiated [(8,11)]. *Streptococcus. pneumoniae* of which there are 92 serotypes, therefore remains the major causative pathogen. *Staphylococcus aureus* and *Klebsiella pneumoniae* are some of the other common bacterial pathogens causing childhood pneumonia [(8)].

The viruses which cause lower respiratory tract infection include RSV, Influenza, Para-influenza virus type III, Rhinovirus, Adenovirus, Bocavirus, Measles virus and Human metapneumovirus, the latter being only recently discovered [(12)]. Of these viruses, RSV and human metapneumovirus which is closely related to RSV, are the most important. Both viruses are enveloped negative stranded unsegmented RNA viruses belonging to the pneumovirinae family of viruses and the paramyxoviridae subfamily [(13)].

An approach to community acquired pneumonia categorised according to aetiology by Gessman et al [14] is depicted below:

- Neonates: Group B streptococcus, Gram negative bacteria, CMV, HSV.
- Infants: *Chlamydia trachomatis* (greater than) >3 weeks S-pneumonia.
- School going children: *Chlamydia pneumoniae, Mycoplasma pneumoniae*.
- Preschool children: Viruses, *Streptococcal pneumoniae* and *Mycoplasma pneumoniae*.

Distinguishing typical bacterial pneumonia from atypical (viral) pneumonia clinically in children is difficult as both exhibit similar symptomatology and signs [10]. Likewise, because the spectrum of disease caused by pathogenic respiratory viruses is so similar it is clinically difficult to distinguish which causative virus is involved.

Diseases caused by respiratory viruses include; pharyngitis, otitis media, laryngitis, bronchitis, tracheitis, bronchiolitis and pneumonia. The most common manifestations of lower respiratory tract infection are bronchiolitis and pneumonia [15]. Symptoms such as conjunctivitis, otitis media and wheezing have been shown to be more common in viral rather than bacterial pneumonia. Interestingly, although myalgia and rhinorrhoea are linked to viral infection, these symptoms are not commonly associated with viral pneumonia [10]. The most significant signs which are helpful in differentiating a bacterial from a viral pneumonia include: high fever (greater than) >38° degrees celcius and pleural effusion that signify bacterial infection [14].

A study done by Williams et al showed that children who had pneumonia which was complicated by pleural effusion either had S. pneumoniae as the causative agent or S. aureus with influenza virus co-infection. The study demonstrated that in the latter group, the pneumonia was more severe [16]. Mc Nally et al in their study aimed at determining the effects of polymicrobial disease, on severe pneumonia and treatment response also concluded that polymicrobial disease was a significant factor in determining treatment failure; those with this type of infection thus had a higher risk for mortality [17].

X-rays have been shown not to be a useful diagnostic tool in the assessment of pneumonia less than 5 years of age. Not only is there a poor correlation between x-ray and clinical findings and the aetiology of the pneumonia but there are also differences in interpretation of the radiographs. These differences mainly concern the issue of infiltration versus consolidation [18,19].

<u>RISK FACTORS FOR LOWER RESPIRATORY TRACT INFECTION</u>

The risk factors for lower respiratory tract infection includes lack of breast feeding, malnutrition, upper respiratory tract infection in the mother and siblings, immunization status [20], indoor exposure to vitiated air and overcrowding. [2, 21, 22] Overcrowding (large families living in small houses) is invariably associated with low socio-economic status and lower education [23]. The recommended average living space per person according to the WHO recommendation is $12m^2$ [24]. In many developing countries and also in certain

locations in the Western Cape, the size of the living space is reduced to below the WHO recommended parameters ([23]. Overcrowding is known to increase the risk of transmission of both bacteria and viruses. A study done by Cardoso et al in Sao Paulo found that in cases of crowding where more than 4 people shared the child's bedroom, the risk of lower respiratory tract infection increased 2.5 times [24].

Exposure to cigarette smoke predisposes to night time cough, bronchitis, bronchiolitis and pneumonia in the first two years of life [25]. Prenatal and post-natal tobacco smoke exposure in addition to the aforementioned increases the risk of childhood otitis media and asthma. The severity of these diseases is directly linked to increased smoke exposure [26].

A study done by Singleton et al [27] showed that low birth weight in all racial groups was a major risk factor for lower respiratory tract infection. Low birth weight infants are predisposed to lower respiratory tract infection as they are more likely to have impaired respiratory function and immunocompetence [22]. Iron deficiency anaemia amongst Lebanese children was also found to be a risk factor [28].

Children living in low/poor socio-economic communities are more at risk for severe pneumonia as these circumstances are known to be associated with malnutrition and restricted health care [29].

A study done by Roth et al found zinc supplementation to decrease the incidence of acute lower respiratory tract infection, however, vitamin A was found not to decrease the incidence beyond the neonatal period [30]. Zinc has been shown to decrease RSV replication, this mechanism being highly dependent on the concentration. Ten micromoles of zinc caused an 800 times decrease in RSV replication rate, whereas a higher zinc concentration was found to be harmful to epithelia [31].

In a commentary by Paynter et al it is stated that childhood pneumonia generally is associated with climate change. The incidence of pneumonia was shown to increase during rainy seasons. This is attributed to prolonged bacterial survival and overcrowding and smoke exposure which took place during this period. The climate change which is also associated with food shortages during which time, malnutrition occurs [32].

Pearson et al demonstrated that some of the avoidable factors associated with both natural and unnatural child death cases were failure to recognize serious illness by way of omitting to examine the child, failure to correctly interpret physical signs and to foresee complications by either a health service or by a primary care giver. The most significant recurrent factor was failure to recognize severe illness at a health service [33].

RESPIRATORY SYNCYTIAL VIRUS

RSV is the major cause of lower respiratory tract infection in infancy and children globally. It is the most significant cause for hospital admission in infancy and childhood in developed countries. In the United states, RSV lower respiratory tract infection accounts for 85 000 to 144 000 infant hospital admissions yearly. Seventy percent of these admissions are due to RSV bronchiolitis and 20-25% are due to RSV pneumonia[34].

RSV and RNA virus encodes for approximately 10 viral proteins. Amongst the protein encoded are three transmembrane glycoproteins namely fusion glycoprotein-F, an attachment glycoprotein- G, and hydrophilic glycoprotein-SH. The G protein allows the virus to attach to cell membranes whereas the F protein allows for viral penetration of the cell and fusion of infected cell membranes. This gives rise to syncytial formation, the characteristic feature associated with the virus [35].

The fusion of cell membranes enables viral progeny to spread to adjacent cells. The virus initially infects epithelia in the upper respiratory tract. Viral progeny shed from the apices of infected epithelia is transported to the lower respiratory tract via secretions [36].
Two RSV strains, A and B have been identified. GA3 clade rather than the individual strains is associated with severe disease [37]. RSV is able to rapidly mutate allowing for variability in its G protein and therefore in the given population many RSV variants may co-exist [36].

Bronchiolitis, an acute condition involving inflammation of bronchioles due to viral infection usually occurs in children under 2 years of age. In children who are immune competent the disease is self-limiting. Children with bronchiolitis present with low grade fever, cough rhinorrhoea, wheezing and hyperinflation. The viruses commonly reported to cause bronchiolitis are RSV and Rhinovirus [38]. Rhinovirus has been shown to cause mild bronchiolitis. The virus infects older children of 13 months median age and is associated with atopic dermatitis and eosinophilia. RSV in contrast infects younger children of 5 months median age and causes moderate to severe bronchiolitis.

Risk factors for severe RSV bronchiolitis [13] include.

1. Prematurity
2. Immunosuppression
3. Maternal smoking in pregnancy
4. Absence of breast feeding
5. Low socio-economic status
6. Overcrowding
7. Underlying medical conditions (chronic lung disease, congenital heart disease and Trisomy 21)
8. Ethnicity

A viral infection of the respiratory tract predisposes to bacterial co-infection as it causes destruction of epithelium and increases bacterial attachment [39]. RSV superimposed bacterial infection of the respiratory tract is known to cause severe respiratory illness resulting in hospitalized children needing prolonged ventilation [40,41].

Immuno-compromised children and those who have severe RSV infection are more at risk for bacterial co-infection [38]. The incidence of RSV and bacterial co-infection has been reported to be between 17.5 and 44%. [40,42]

In a study conducted by Hishiki et al the pathogenic bacteria isolated from sputum of children infected with RSV included non beta lactamase producing H influenzae (43.9%), S.pneumoniae (36.6%) and M. catarrhalis (29.3%).[43] Immunocompromised children and those who have severe RSV infection are more at risk for bacterial co-infection.[38]

There is an association between RSV outbreaks and the weather. RSV outbreaks are said to be highly predictable [5] occurring in the winter in temperate climates and in the hot rainy seasons in tropical countries [38]. In cold weather children stay indoors and in circumstances of overcrowding there is an increased rate of RSV infection. In humid conditions the virus survives for a longer period of time as it is less prone to desiccation [44]. In South Africa however RSV outbreaks show both seasonal and regional variability. Because the virus in HIV infected children is shed over a prolonged period of time it may be found in these children throughout the year and is not confined to a specific season. In HIV uninfected children, the virus is shed usually over a 5 to 7 day period [38].

The factors initiating RSV epidemics to date are still poorly understood. It is considered to be related to climatic factors, e.g. temperature [35] and factors related to altitude and latitude [38]. Al-Toum et al theorise that the outbreaks may be associated with staying indoors during cold weather, which enhances its spread.[5].

RSV is highly contagious and is spread by direct inoculation of infected aerosol particles into either the eyes or nose. Large aerosol particles emanating from either a cough or sneeze spread the virus within a 3 feet radius, whereas small aerosol droplets are less likely to spread the virus long distances [46].

Infected secretions may also be spread by hand to hand contact. More notable is that the virus may be spread by means of contact with various contaminated surfaces. The virus remains viable for a period of time on different types of surfaces, e.g. 45 minutes on cloth, 20 minutes on skin and approximately 6 hours on table tops [38, 46].

The RSV incubation period is 3 to 8 days, the average being 5 days. The nasal and eye mucosa is more sensitive to infection compared to that of the mouth [15]. The virus replicates in the respiratory epithelium, the ciliated columnar epithelium being its primary target. Replication however may also occur in the intra-epithelial dendritic cells [46].

Bronchioles of infants are of a small diameter. These dilate on inspiration and collapse on expiration. The bronchioles of infants, given their small diameter and given that air flow resistance is inversely proportional to the cube of the bronchiole lumen radius, are at risk for obstruction. When there is partial luminal obstruction, a ball valve effect occurs whereby air may be inhaled but not exhaled. This results in air trapping and hyperinflation. The entrapped air may ultimately be absorbed causing lung atelectasis. In the setting of bronchiolitis the lumens of inflamed, oedematous bronchioles ultimately become obstructed by mucus, shed respiratory epithelium and necrotic cellular debris [46,47].

The severity of RSV infection is related not only to an individual's genetic make up, age, and previous RSV exposure, but also to the immune response to the viral infection. During RSV infection, antibodies are directed against both the F and G-proteins. In infants under 6 months of age, the antibody response to the viral F-protein is not optimal, in contrast to that in infected older children [46]. In animal models, inflammatory cells are recruited to RSV infected airways, mediated by chemokines and cytokines. Interleukin 4, 8, 9 and Interferon gamma have been identified in the respiratory secretions of infants suffering from severe bronchiolitis [48,49].

The cellular immune response when suppressed is associated with severe disease and protracted viral shedding. In-vitro, repeated and primary RSV infection, is considered to impair RSV specific T-helper cell responses; dendrites which are infected by the virus demonstrate impaired function in activating CD4+ T-cells. Furthermore, apoptosis of CD4+ and CD8+ lymphocytes has been identified in infants suffering from RSV bronchiolitis [46].

According to a study done by Johnson et al [47]., the following histopathology was evident in fatal untreated RSV infection:

a. RSV infected the epithelium of "small bronchioles" in a circumferential manner, sparing the basal cells. RSV also infected both type 1 and 2 pneumocytes.
b. A distinct pattern of distribution of inflammatory cells:
   - Neutrophils were most prevalent between airways and arterioles while mononuclear cells were found in the airway and lung parenchyma. Of these, the majority infiltrated beneath the lamina propria however many did transgress the mucosa and were found in the lumen of the airway.
   - The most prevalent cell type present around bronchioles and pulmonary arteries were monocytes which stained CD69+. The second most prevalent cell type was CD3 T lymphocytes
c. Obstruction of bronchioles is caused by the presence of epithelial projections (syncitial giant cells), fibrin, mucus, oedema, inflammatory cells and bronchiole epithelial cells in their lumens. Bronchiolar obstruction is also due to hyperplastic lymphoid follicles compressing their lumens.

   The syncitial giant cells seen in RSV infection may mimic those seen in measles pneumonia. The bronchial epithelium and alveolar pneumocytes may also contain cytoplasmic inclusion bodies [50].

   Pulmonary haemorrhage has been described in cases of both bacterial and viral infection of the lung. Its cause is unclear. It is considered to be possibly related to acute left ventricular failure which causes increased pulmonary capillary pressure. [51] Viral infections characteristically produce "cytopathic-cytoproliferative" inflammation manifesting as either cell necrosis or proliferation.[52]

   Diffuse alveolar damage (acute lung injury) is a pattern considered to be one of the important manifestations of infectious disease, and specific viruses which cause this include RSV, measles, influenza and adenovirus. Diffuse alveolar damage manifests as pulmonary oedema and pulmonary haemorrhage. [53]

SUDDEN UNEXPECTED DEATH IN INFANCY AND SUDDEN INFANT DEATH SYNDROME

Beckwith defined SIDS (Sudden Infant Death Syndrome) at an international conference in Seattle in 1969 as a "sudden unexpected death of an infant or young child, the cause of which remains unascertained despite a thorough post-mortem" [54]

Many definitions have since been proposed, however there has never been a definition of SIDS which has gained universal acceptance. Because of the lack of a standardized definition in autopsy protocols for SIDS the investigation of these death cases is often

problematic. In Australia it emerged that various centres use different protocols and terminology, e.g. SIDS undetermined and unascertained. In March 2004 a workshop held in Australia for the purpose and discussing and adopting a standardized definition and autopsy protocol for SIDS accepted the San Diego definition which is as follows: "the unexpected death of an infant under 1 year of age with an onset of the acute episode apparently occurring during sleep that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history." [55].

HF Krous, one of the leading experts in SIDS considered it imperative that the SIDS definition be constantly reviewed and revised as researchers knowledge about the condition expands. He also suggests that the type of pathology in infant sleep environment commonly associated with SIDS be integrated into its definition [56].

Peter Sidebotham in his commentary on SUDI (Sudden Unexpected Death in Infancy) and the dilemma of defining the SIDS (Sudden Infant Death Syndrome) by Henry Krous, notes that although Henry Krous advocates constant, steadfast revision of SIDS definitions, that would meet approval worldwide, there was over the past 20 years never any worldwide "acceptance" of the definition. He notes further that "standards for investigation in different countries will vary" and that "the complexity of understanding SIDS has the potential to increase rather than decrease." He personally prefers the broad term SUDI "the death of an infant which was not anticipated as a significant possibility 24 hours before death" and after the death investigation described the death as being
1-explained SUDI,
2-unexplained SUDI (SIDS).

This approach according to Sidebotham has gained increasing credence and acceptance in the United Kingdom [57].

The investigation into SUDI calls for an integrated approach which not only involves performing a thorough autopsy based on the standardised protocol, but also interaction with local child protection agencies and social and health services [58]. In some countries however due to religious, legal and political constraints, this type of investigation into SUDI cases might not be possible [59].

The protocol for an autopsy on cases of SUDI proposed by Howatson [60] includes the following:

1. Obtaining information regarding the scene of death
2. Obtaining information regarding the circumstances in which the death occurred
3. Obtaining information regarding antenatal and obstetric history
4. Obtaining information regarding resuscitation procedures involved
5. Performing full body X-rays
6. Doing an external examination of the body and assessing growth parameters
7. Assessing dysmorphism
8. Examining all orifices and assessing whether or not there is evidence of metabolic disease, i.e. an enlarged heart and liver, muscle pallor and cerebral oedema
9. Performing biochemical analyses to assess dehydration and metabolic disease, microbiology and neuropathological examination is also advocated.
10. Performing histological examination of tissues.

In this protocol ophthalmic examination is advocated in and restricted to cases where a diagnosis of head injury has been made clinically.

The protocol put forward by Gould [61] is similar to that proposed by Howatson. Histological examination of tissue is considered mandatory but workup for metabolic disease according this protocol is to be based on discretion and should be considered in cases where a sibling had died previously and fat is present in muscle, liver and kidneys.

The causes for death in cases of explained SUDI as determined by the CESDI study [62] is depicted below, having accounted for an estimated 20% of SUDI cases:

1. Respiratory system: bronchiolitis and pneumonia
2. Central nervous system: meningitis, trauma, other
3. Cardiovascular system: myocarditis , congenital anomaly
4. Gastro-intestinal system: obstruction: volvulus, intussusception, gastro-enteritis
5. Other: septicaemia, metabolic disorders
6. Trauma/accident.

A study done by Weber and Ashworth over a 10 year period on autopsy data of cases of SUDI ages 7 to 365 days, determined 37% of death cases to be explained and 63% to be unexplained. Histological examination of tissue was found to be the most valuable investigation in determining cause of death. It revealed cause of death in 46% of cases compared with macroscopic examination and microbiology which yielded a cause for death in 30% and 19% of cases respectively [63].

There is no constellation of autopsy findings which constitutes the diagnosis of SIDS. Externally the infant's face may be either pale, congested, or mildly cyanosed. Subcutaneous and subconjunctival petechial haemorrhages are not a feature in these cases. There may be nasal and circumoral pallor where pressure has prevented post-mortem lividity from occurring in these regions, however this should not be misinterpreted as being due to smothering in cases where the body of the infant is found in a face down position. The position in which the child had initially been put to sleep may be more significant. There may be some froth present in and around the lips and nose. Gastric content may be present in the airway. This may be due to "agonal regurgitation" and need not necessarily be a cause for death [64]. Bernard Knight had personally found gastric content regurgitation in 25% of autopsy cases where a diagnosis for death due to other pathological process was present.

Mucosal inflammation according to Bernard Knight was not a common finding in SIDS cases. He states categorically that if respiratory infection is "severe enough to produce pus and especially if there are obvious inflammatory changes in the lung parenchyma" the diagnosis of SIDS cannot be made. Small foci of lymphocytes have been shown to be present in control cases and therefore if present in SIDS cases should be disregarded. This is highlighted in a study conducted by Henry Krous [65]. This study compared the amount of lymphocytic infiltration around bronchioles and within the lung interstitium in SIDS cases, to that in cases of accidental and inflicted death, and demonstrated there to be no significant difference amongst them. It was thus concluded that a minimal inflammatory infiltrate in these areas did not cause fatality.

Microbiological cultures in SUDI cases often yield bacteria which are not linked to the cause of death, however in a large proportion of unexplained SUDI cases, S. aureus and E. coli were cultured and are thus considered to be linked to cause of death [66]. S.

aureus -specifically toxogenic S. aureus, is considered to cause toxic shock syndrome which results in exaggerated inflammation and cytokine production, hypothermia, hypoglycaemia, cardiac arrhythmia, anaphylaxis and hypoxia [67]. This is supported by a study done by Goldwater et al which also demonstrated the presence of S. aureus in SIDS cases in sites which are normally sterile, i.e. heart, blood, spleen and CSF [68].

A study conducted by Weber et al [69] showed pathogenic viruses in only 2% of SUDI cases. The detection of viruses in this study by means of immunofluorescence was found to be low. PCR however was found to be a better technique for the detection of viruses. Viruses were found to be present in both explained and unexplained SUDI cases and their isolation rate was similar in these two groups. From this, it was deduced that the presence of viruses in the absence of pathology or symptoms is in keeping with a carrier state.

SIDS cases are known to peak during the second and third month of age and then decrease. It is rare within the first month of life. There has been since 1992, a steady decline in the SIDS rate in the United States, the death rate in that year being recorded as 1.20/1000 live births to such an extent that in 2001, it was recorded as 0.56/1000 live births. This suggests a 53% reduction and is considered to be due to decline in the prone sleep position [70].

Numerous studies have consistently identified the following as risk factors for SIDS [70].

1. Prone sleep position
2. Sleeping on soft bedding/surface
3. Antenatal smoke exposure
4. Overheating
5. Late or no antenatal care
6. Young mothers
7. Males
8. Ethnicity: American Indian and Alaskan Native children

Other risk factors for SIDS as depicted by Moon et al [71] are as follows:

1. Exposure to tobacco smoke
2. Prone or side positioning
3. Usage of a pacifier
4. Room sharing, not necessarily bed sharing
5. Immature cardio-respiratory autonomic control
6. Failure of sleep arousal

Another study has shown pacifiers to decrease the risk of SIDS by altering the anatomy of the upper air passages; sucking on a pacifier according to the authors stimulates growth of “neural pathways” involved in maintaining a patent upper airway passage [72].

Maternal psychiatric disorders such as depression and schizophrenia may also be risk factors as these disorders are not only associated with smoking and substance abuse (smoking itself being an independent risk factor) but also with suboptimal infant care [73].

The prone position may predispose infants to asphyxia when there is airway compression and rebreathing of exhaled gases. Hyperthermia may also occur when their faces are

"pressed against bedding" [74]. In this setting the arousal mechanism in response to the asphyxia is abberant.

Exposure to both maternal and paternal cigarette smoke are risk factors for SIDS, the maternal cigarette smoking being more disadvantageous than the paternal cigarette smoking [75]. Prenatal tobacco smoke exposure has been demonstrated to decrease birth weight and disrupt foetal brain stem and serotonergic receptor site development. Serotonin is involved in autonomic control of heart rate, arousal and respiration and is therefore of interest in SIDS cases [76]. Low birth weight and post-natal exposure to cigarette smoking are independent risk factors for SIDS. Increased post-natal cigarette smoke exposure increases the risk for SIDS [77]. Cigarette smoke exposure is said to increase the risk of infection which in turn results in hyperthermia especially if the infant is put to sleep in prone position or is overdressed [78]. Tobacco smoke exposure also affects lung compliance and volume, and heart rate in circumstances of stress. The nicotine in the smoke decreases the infant's responsiveness to hypoxia [79].

Data regarding infants sleeping in prone position suggest that it decreases their blood pressure and that elevated heart rate does not counteract it. This phenomenon was found not to occur in infants four weeks of age nor five to six months of age but commonly amongst those of two to three months of age when SIDS occurs [80].

Bed sharing has emerged as another risk factor associated with SIDS, however bed sharing irrespective of the position the infant was put to sleep was found by Thogmartin et al to be more prevalent in unexplained SUDI (SIDS) [81].

A relationship between prone sleeping and viral infection has been proposed. Given that viral infection predisposes to superimposed bacterial infection, placement of a feverish child to sleep in prone position would increase the production of secretions which, with increased temperature are conducive for the production of bacterial toxins. This, associated with aberrant cytokine production, is considered to be a possible mechanism for SIDS [82].

A study done by Vennemann et al [83] to evaluate the differences in risk factors between explained SUDI and SIDS demonstrated that lower socioeconomic circumstances and maternal smoking were associated with both of these entities. However prone sleep position and lack of breast feeding were found to be solely related to SIDS.

The epidemiological factors related to SIDS such as being male, low birth weight, short gestational age, single mother, multiple pregnancies and the period during which SIDS occurs, 4 to 16 weeks, have not, according to a study done by Leach et al changed [84]. The study identified three significant profile differences between SIDS and explained SUDI namely:

1. the age distribution is different; SIDS cases peak between 4 and 16 weeks compared with the explained death cases which peaked between birth and two months and remained constant thereafter.
2. the incidence of congenital anomalies is higher amongst explained SUDI compared to SIDS
3. the incidence of maternal cigarette smoke exposure was found to be significantly higher among SIDS cases compared to cases of explained SUDI.

It is not possible to distinguish death due to true suffocation from SIDS victims, given that the pathology is so similar [64]. With regard to SIDS in siblings, Di Maio is quoted as saying "more than one SIDS death should evoke suspicion of homicide" but both Krous and Byard can counter this argument by pointing out that similar risk factors and genetic aberrations which resulted in the first SIDS case may in all probability affect siblings [85].

Genetic risk factors for SIDS have been identified, i.e. genetic polymorphism involving the serotonin transporter and the cytokine interleukin 10 These genes are involved in the autonomic control of cardiac and respiratory function [86,87].

Kinney etal [88] propose that "SIDS is state-related, and results from a brain abnormality in the state-modulated regulation of cardiopulmonary mechanism. This brain abnormality is further postulated to originate in utero and lead to sudden death during a vulnerable postnatal period. They also propose a triple risk model for SIDS which advocates the interplay of three factors namely a vulnerable infant, a critical developmental period and an exogenous stressor e.g. prone sleeping.

Another risk factor for SIDS is prematurity. Infants born late preterm, 33 to 36 weeks gestational age were found to have double the risk of being a SIDS victims than infants born at term. [89,90]

Gastric content may be found in the airway in some infants who have died in a sudden manner [91]. In a study conducted by Nishi et al, it was demonstrated that this material did not cause nor contribute to asphyxia in any way as it was found to be of insufficient quantity. It was thus concluded that it was either a post-mortem artefact or that "passive" gastric content aspiration occurred agonally[92].

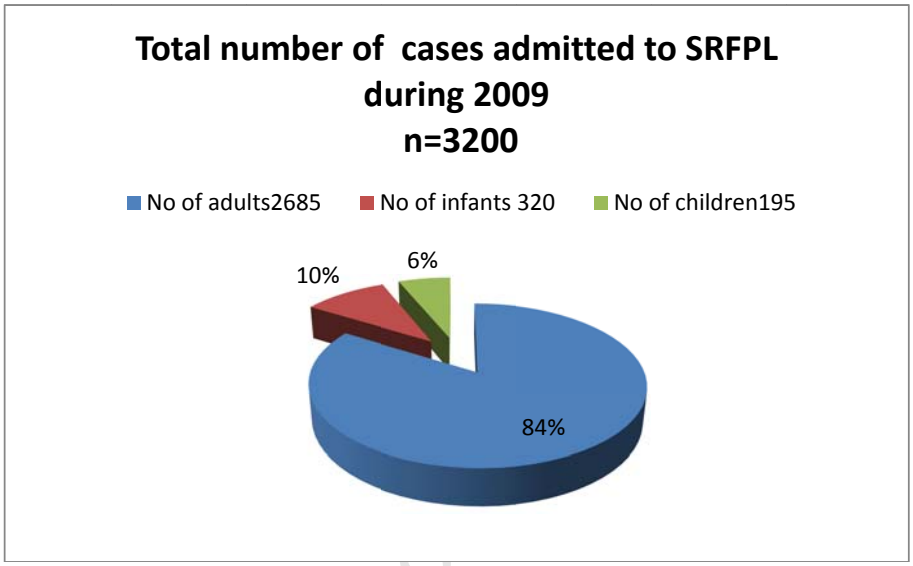
The neuropathology associated with SIDS as depicted in the text book titled "Neuropathology by Greenfield" in a chapter authored by Rebecca D. Folkerth and Hannah C Kinney[93] is as follows: "Increased brain weight, subtle brainstem scarring, altered dendritic spine density density development in the brain stem, increased synaptic density in the central reticular nucleus of the medulla, altered brain stem neurotransmitter parameters, subtle hypomyelination within and rostral to the brain stem, cerebral white matter gliosis, peri-ventricular leucomalacia, increased neuropil in the hypoglossal nucleus, increased lipid containing cells in the cerebral white matter, delayed development of the cervical vagus nerve, increased substance P, delay in the maturation of the external granular layer of the cerebellum and inferior olivary abnormalities."

A study conducted to determine the incidence of the various causes of SUDI highlighted the need for a thorough post-mortems to be done by pathologists with paediatric expertise so as to more reliably diagnose possible metabolic and neurological syndromes which could have caused SUDI. The non-SIDS diagnoses in SUDI cases were found to be proportionally higher when a pathologist with paediatric expertise performed the histologic evaluation. It also suggested that studies on entire populations provide more reliable data on SUDI than small group studies [94].

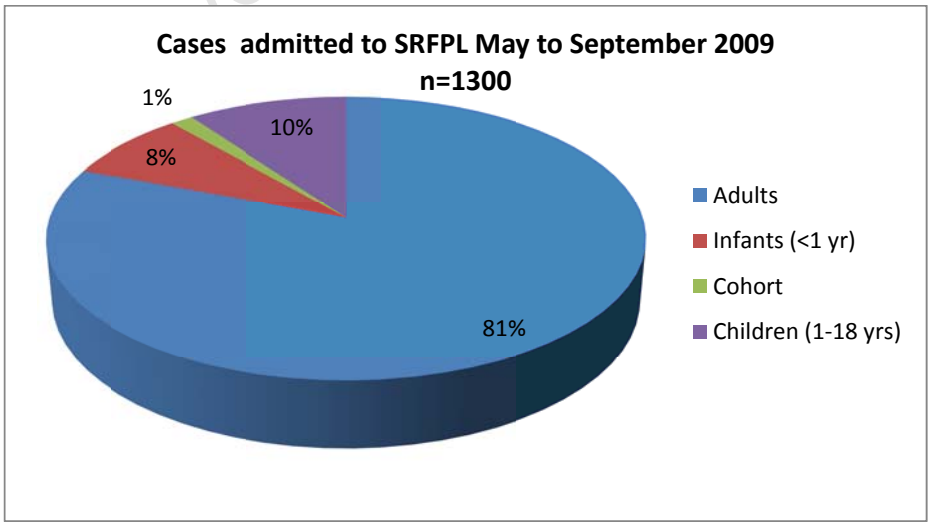
Chapter 3

OVERVIEW

The SRFPL in 2009 admitted a total number of 3200 death cases (both adult and child death cases). Of this, there were 515 child death cases i.e. those under 18 years, of which 320 were infants i.e. those under 1 year of age. This is depicted in Fig 1 below.



249 of the total number of child deaths (515 cases), occurred during the study period May to September 2009. Of the 249 child deaths, there were 120 infant deaths. Of the 120 infant death cases, 18 cases were identified for the cohort. This is depicted in Fig 2 below



Chapter 4

RESULTS

The cohort consisted of 18 infant death cases. In 13 cases, the infants demonstrated no symptoms of any kind prior to death. In 5 cases, the symptoms were allegedly minor such that the infants were considered to be "well".

The examination of the external body of cases in the cohort showed no evidence of ante-mortem injury.

X-ray examination of the entire body showed no bone fracture.

The following figures (3, 4 and 5) depict the gender, race and age distribution in the cohort of 18 cases.

As is evident, male infants outnumbered female infants. There were no Caucasian, nor Indian nor Asian infants in this cohort, the African infants accounting for the majority (77.8%) of death cases. Most infant deaths occurred between 1 and 3 months accounting for about a third of the proportion of deaths (61.1%).

Fig 3

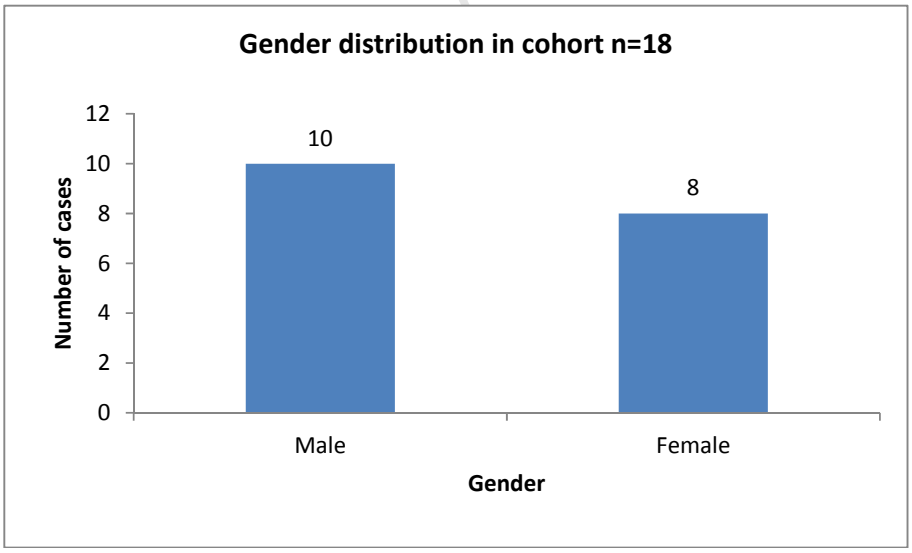


Fig 4

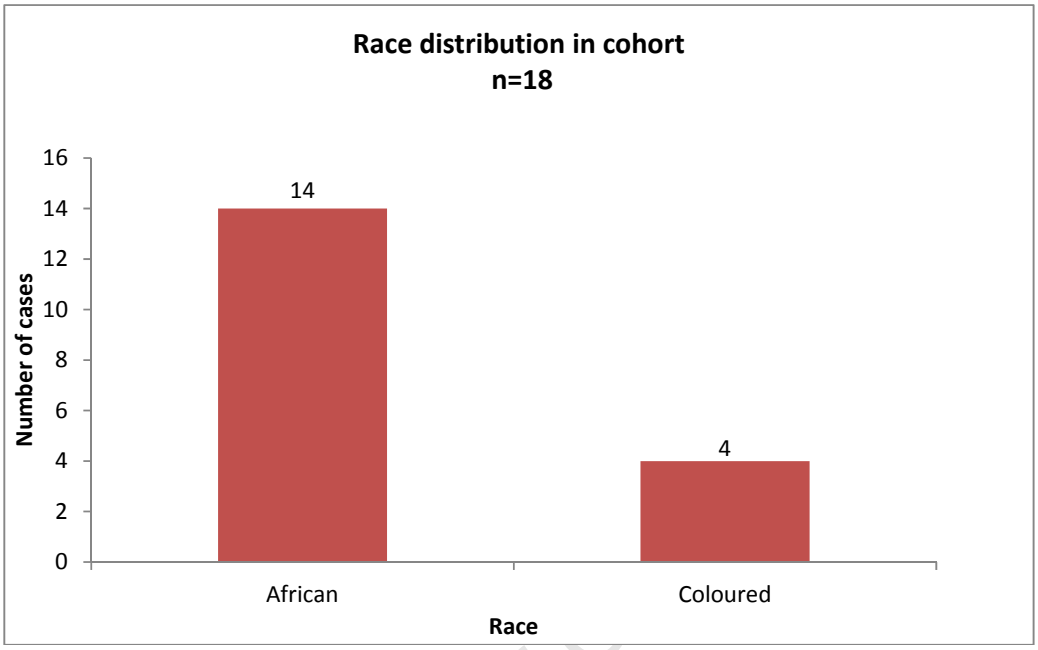
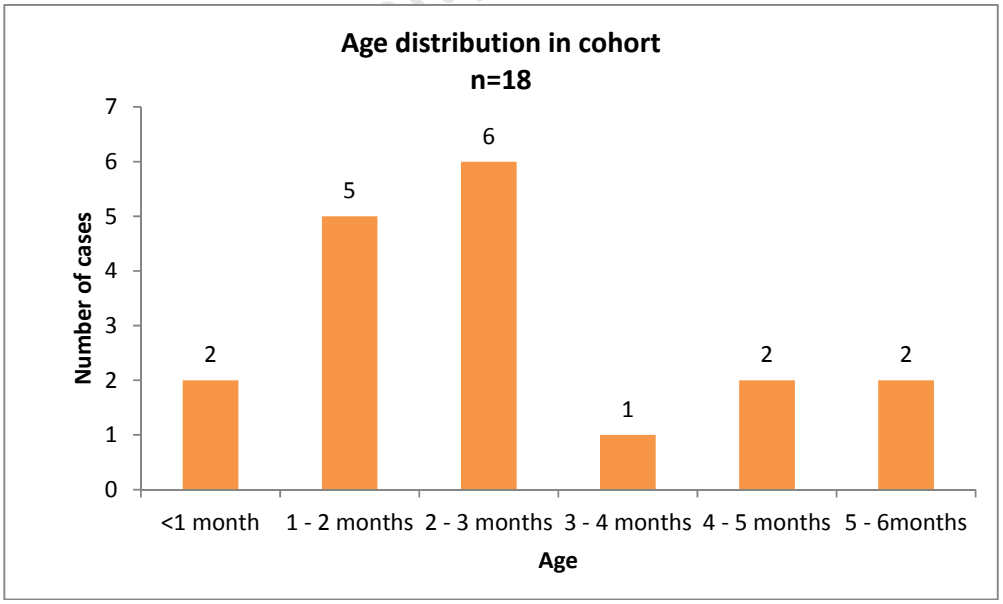

Race distribution in cohort
n=18
Number of cases
16
14
12
10
8
6
4
2
0
14
4
African
Coloured
Race

Fig 5

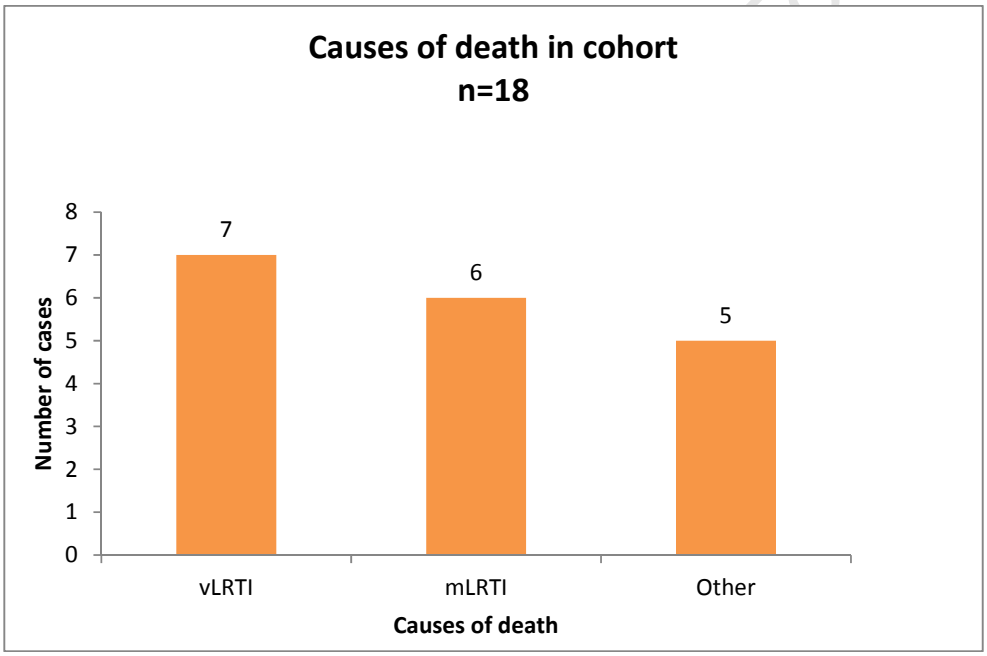

Age distribution in cohort
n=18
Number of cases
7
6
5
4
3
2
1
0
2
5
6
1
2
2
<1 month
1 - 2 months
2 - 3 months
3 - 4 months
4 - 5 months
5 - 6months
Age

CAUSES OF DEATH

Fig 6
The figure below depicts the causes of death in the cohort. As is evident, death due to lower respiratory tract infection (viral and polymicrobial type) accounted for 72.2% of all causes of death. With reference to Annexure 7, these included 13 cases i.e. cases 1,3,5,6,8,9,10,11,12,13,15,17 and 18.

The other causes of death with reference to Annexure 7 included 5 cases i.e. cases 2, 4, 7, 14 and 16. There were 4 cases of viral meningitis one of which was associated with myocarditis and 1 case of gastric content aspiration which was associated with intra-pulmonary haemorrhage.

There were no deaths due to either purely bacterial or mycobacterial lower respiratory tract infection in this cohort.



Of the 7 cases of viral lower respiratory tract infection (cases 1, 3, 6, 8, 13, 15, 18), 1 case (case 1) demonstrated a cough for less than 24 hours. There were no symptoms associated with the other cases.

Of the 6 cases of polymicrobial/mixed lower respiratory tract infection (cases 5, 9, 10, 11, 12, 17), 2 cases (cases 5 and 9) demonstrated minor symptoms (cough and runny nose) prior to death. See Annexure 6.

Of the 5 cases where deaths were not due to lower respiratory tract infection, there were 2 cases (cases 4 and 14) which demonstrated minor symptoms (cough and fever). See Annexure 6.

VIRAL PATHOGENS

Six of the eighteen cases in the cohort yielded a positive viral culture (33.3%). With reference to Annexures 3 and 7, this pertains to cases 1, 11, 12, 14, 17 and 18. The majority of positive cultures came from deaths due to lower respiratory tract infection (5 of the 6 positive cultures).

Of deaths due to polymicrobial/mixed type of lower respiratory tract infection (6 cases), there were three positive culture results. The viruses cultured included:

Case 11. Parainfluenza virus
Case 12. Human metapnuemovirus
Case 17. Adenovirus and RSV

Of deaths due to viral type lower respiratory tract infection (7 cases), there were two positive culture results. The viruses cultured included:

Case 1. RSV
Case 18: Para-influenza virus.

Only in one case where the death was due viral meningitis (case 14), was viral culture positive. In this case, a mild lower respiratory tract infection was present. The virus cultured in the lungs here was Human metapneumovirus.

BACTERIAL PATHOGENS

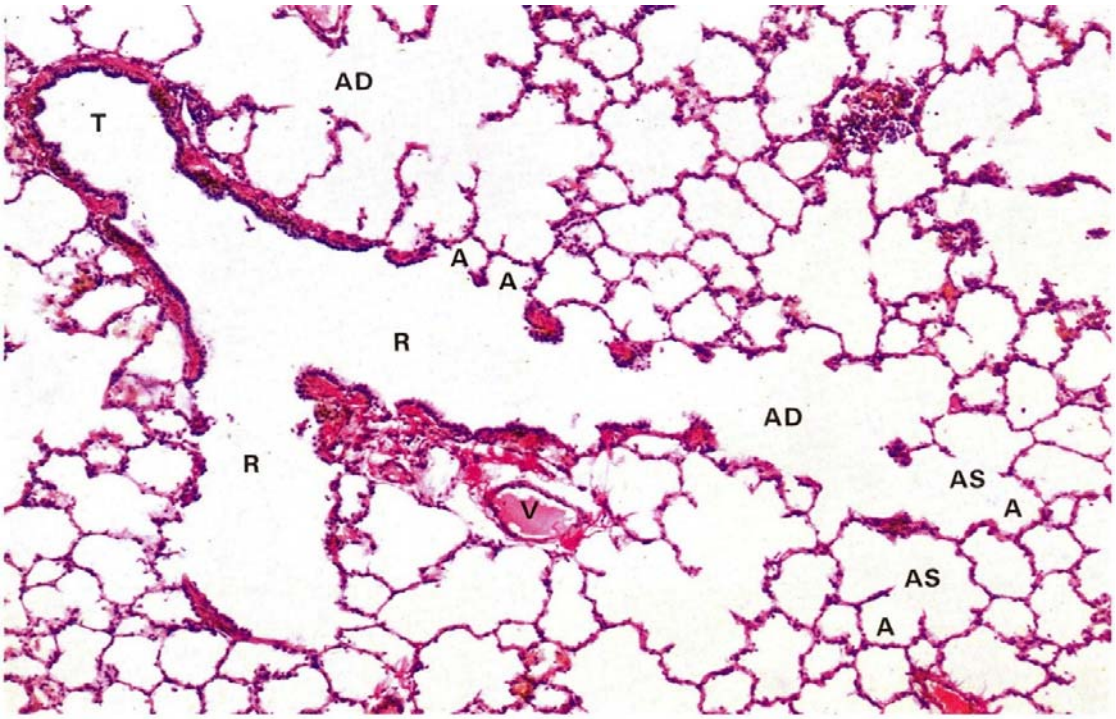
The results of microbiological culture on tracheal secretions in three cases were not available, due to an oversight on the part of the laboratory. Results of microbiological culture of tracheal secretions therefore were available for 10 out of the 13 cases of deaths due to lower respiratory tract infection (76.9%). This pertains to cases 1, 3, 5, 6, 8, 9, 10, 12, 13, 17. All of the cases yielded a mixed growth of organisms.

In case 8, a case of viral lower respiratory tract infection, included in the mixed growth H. influenza was cultured. In case 17, a case of polymicrobial lower respiratory tract infection, S.aureus was cultured. Gram stains done on lung tissue taken for histology in all cases of polymicrobial lower respiratory tract infection proved to be negative.

No case of *Pneumocystis jiroveci* infection was present in the cohort.

The normal lung histology is as depicted below :

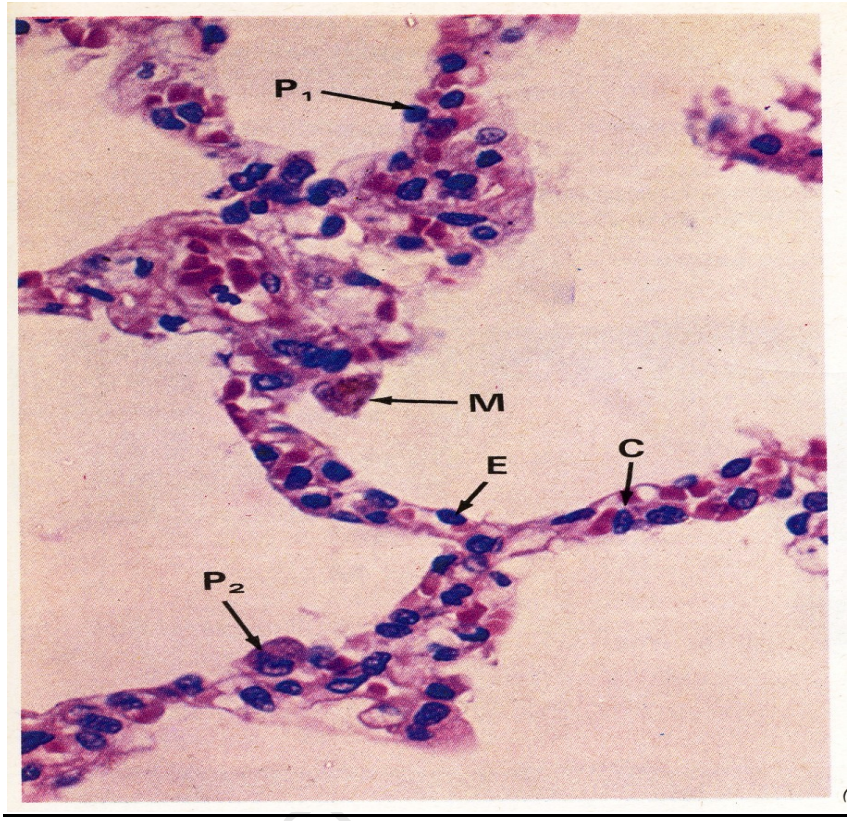
The photograph shows the terminal portion of the respiratory tree at 40x magnification on EVG stain.



Wheater PR, Burkitt HG, Daniels VG. Functional Histology A Text and Colour Atlas pg 166 Churchill and Livingstone, 1979.

T: Terminal bronchiole
R: Respiratory bronchiole
AD: Alveolar Ducts
A: Alveolus
AS: Alveolar Sacs
V: Pulmonary vessel

The photograph below is that of normal alveolus histology with H and E stain at 480x magnification. As is evident in the photograph below there are approximately 8 cells in the alveolar septum located centrally.



Wheater PR, Burkitt HG, Daniels VG. Functional Histology A Text and Colour Atlas pg 167, Churchill and Livingstone, 1979.

P1: Type I pneumocyte
P2: Type II pneumocyte
C: Capillaries
E: Endothelial cell
M: Alveolar macrophage

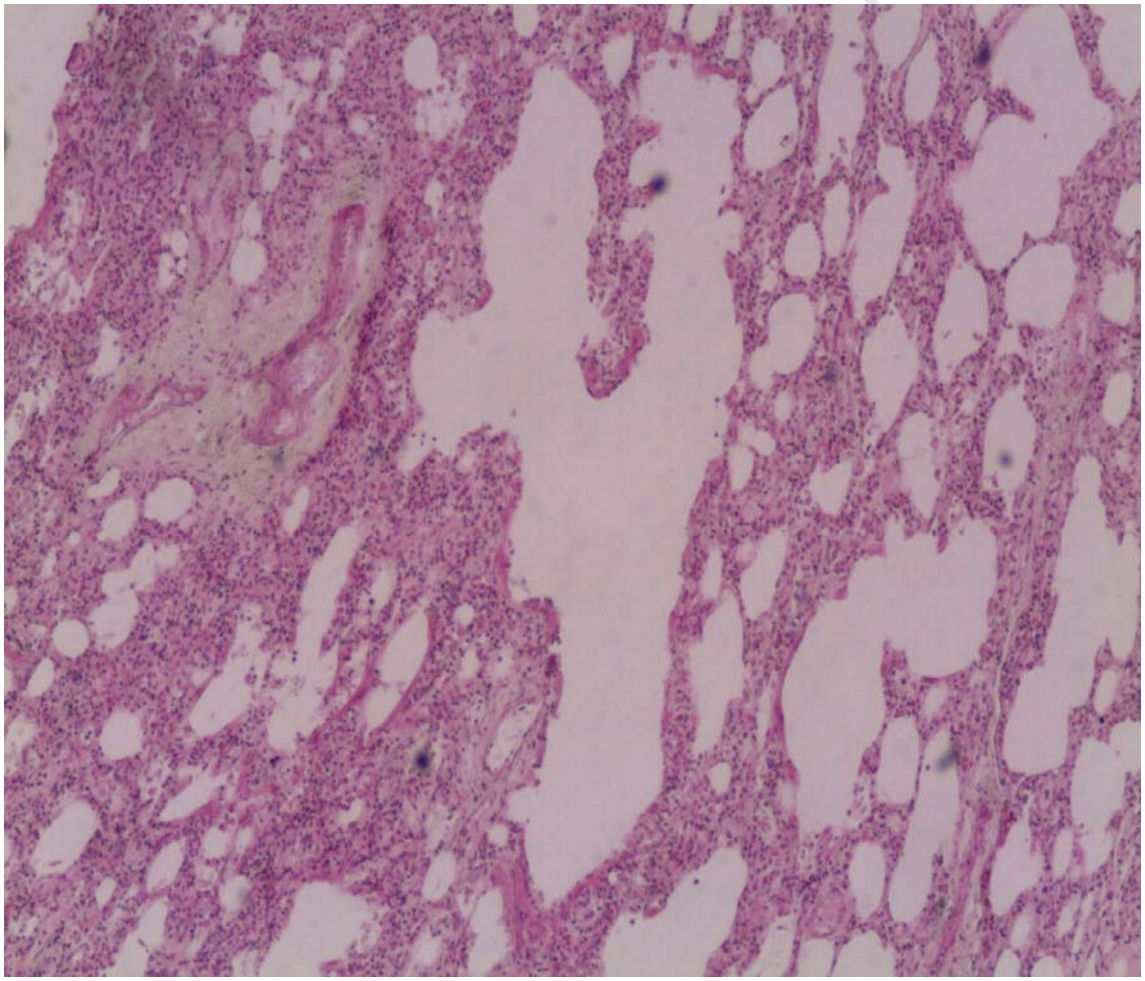
CONTROL CASES SELECTED FOR COMPARISON ARE DESCRIBED BELOW:
Case 1

The deceased is a one year old girl found head down in a 20 litre bucket of drinking water at her home, by her mother. She was retrieved from the bucket and taken to hospital where she was declared dead on arrival there. The cause of death was consistent with drowning.

Lung histology

Five lung sections were examined. In three lung sections there was no bronchiolitis nor interstitial reaction. There was minimal oedema this being present in all sections. Mild bronchitis was present in all the sections.

This is a photograph of one of the lung sections which shows no bronchiolitis.

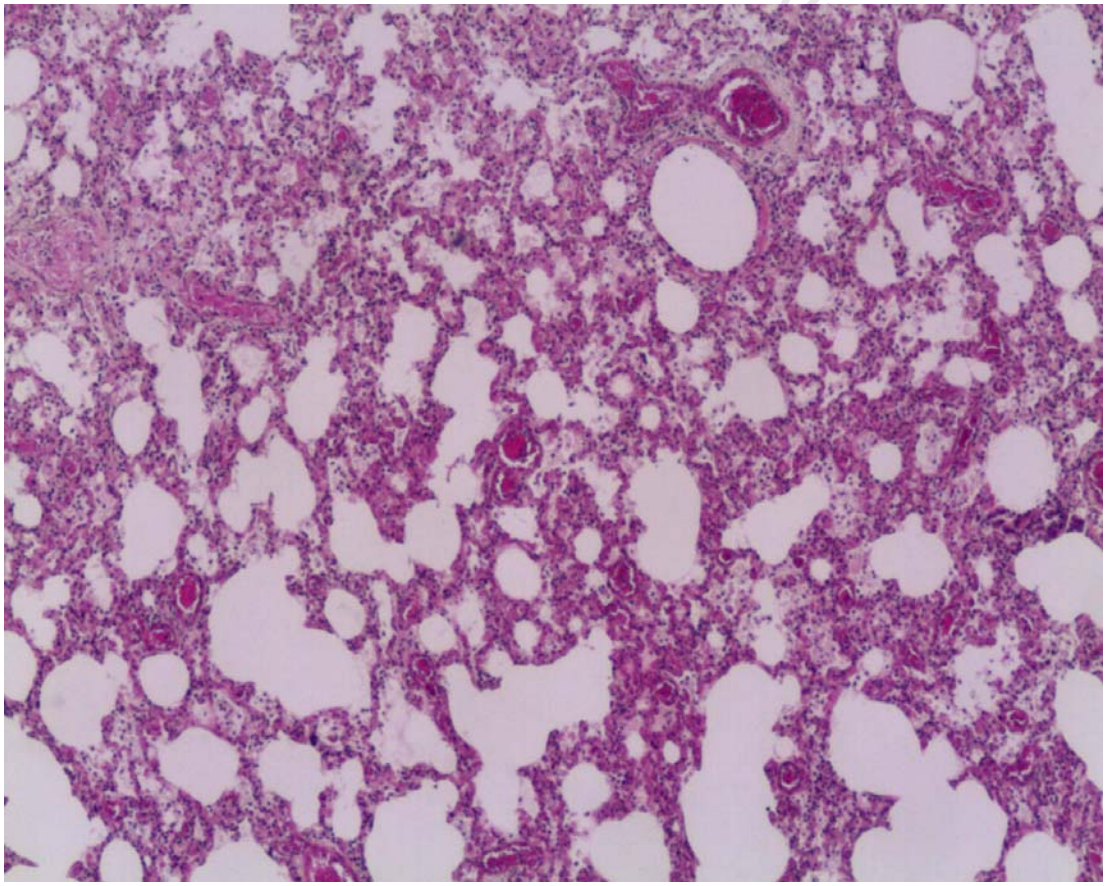


Case 2

The deceased is a 1 year old child who on 2 October 2005, was found in a hole in the ground on a residential premises. The hole was allegedly made for vibracrete (pre-cast concrete) to be inserted. The child was retrieved from the hole and taken to hospital where he was declared dead on arrival. The cause of death was considered to be suffocation and or positional asphyxia after an accidental fall.

Lung histology:

Four Sections were examined. Three showed markedly congested blood vessels, and some intra-alveolar haemorrhage. Intra-pulmonary haemorrhage was present in one section. Bronchiolitis and interstitial reaction was absent. Mild to moderate bronchitis was evident in two sections. This is a photograph of one section which showed vessels congestion and no bronchiolitis,

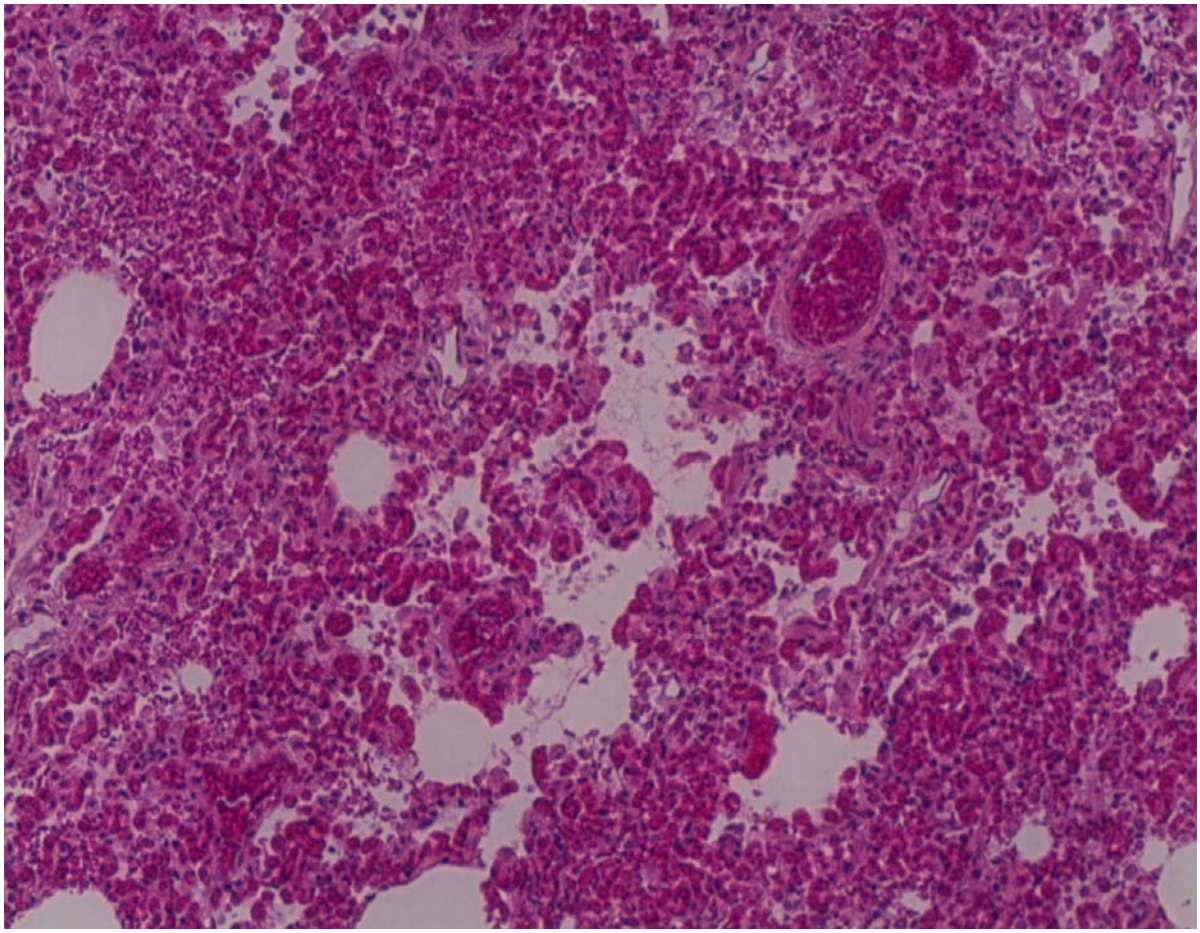


Case 3

The deceased is a 4 month old baby girl who had been well and was found on the floor between the bed and bedside table in a bedroom. The cause for death was considered to be due to positional asphyxia.

Lungs:

Five lung sections were examined. None of the sections showed bronchiolitis, bronchitis or interstitial reaction. There was intense congestion of blood vessels. Pulmonary oedema was minimal. There was patchy intra-alveolar septal haemorrhage present in places in some areas in two sections.

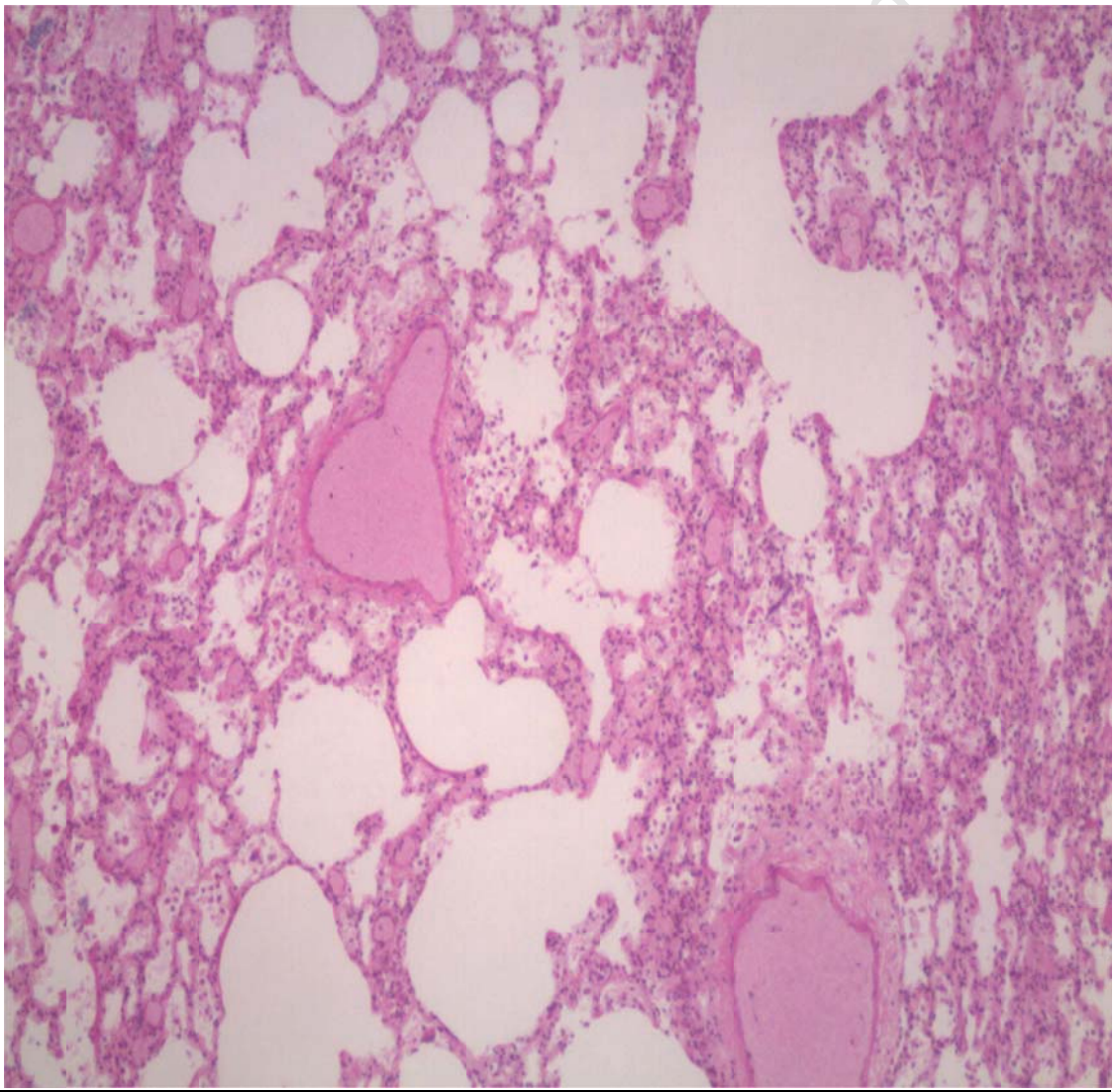


Case 4

The deceased is a 1 year old girl who was poisoned in circumstances of filicide. The poison administered was an organophosphate compound.

Lungs

Five Lung sections were examined. There was no interstitial reaction, nor bronchiolitis. There was mild to moderate pulmonary oedema in all sections. Mild bronchitis was evident in one section. Alveolar space collapse was patchy, but minimal.
This is a photograph from one section which shows no bronchiolitis nor bronchitis minimal oedema and patchy alveolar space collapse.

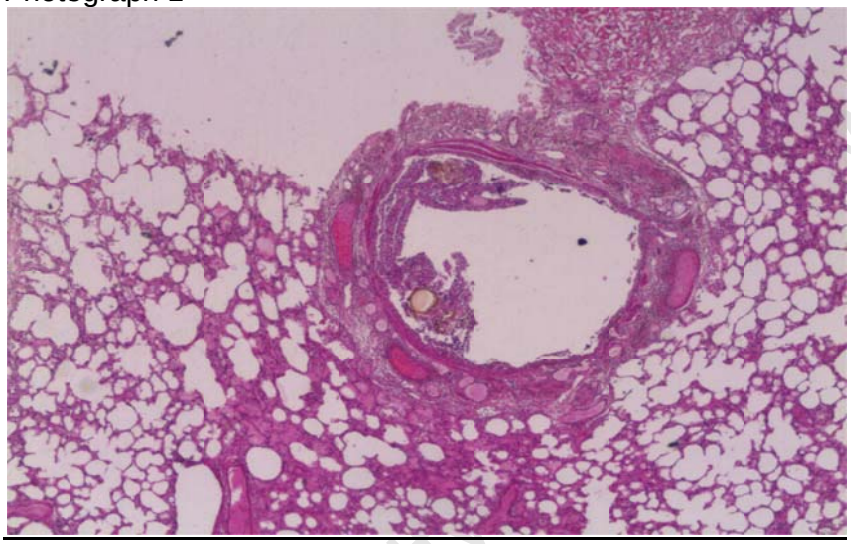


Case 5

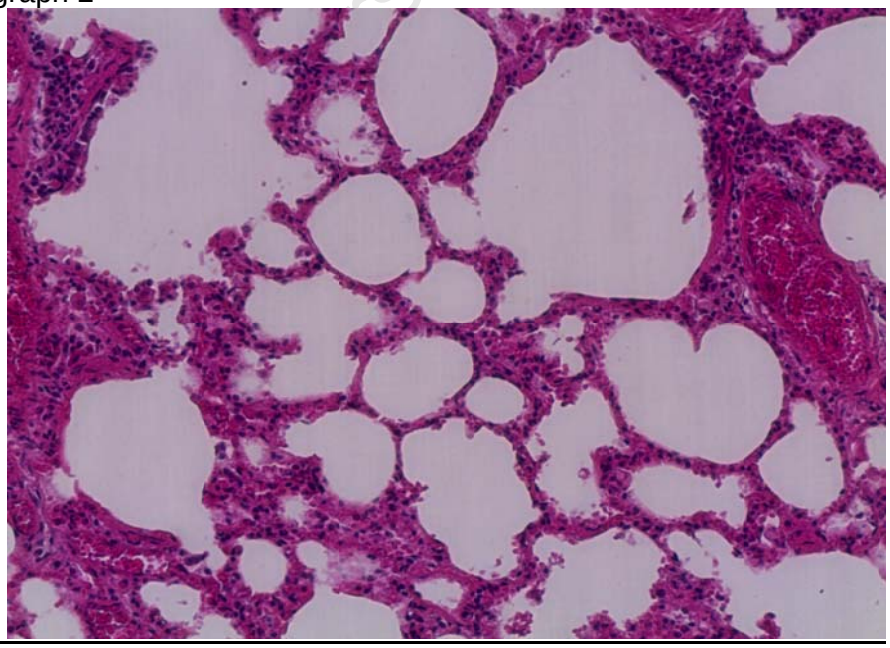
The deceased is a 17 month old boy who was left in a car by the caregiver and succumbed to heat stroke.

Lungs
Four sections were examined. There was evidence of gastric content aspiration as evident in photograph 1. Focal mild bronchiolitis was present in one section as demonstrated in photograph 2. Minimal intra-alveolar haemorrhage was present in one section. Alveolar space collapse was minimal.

Photograph 1



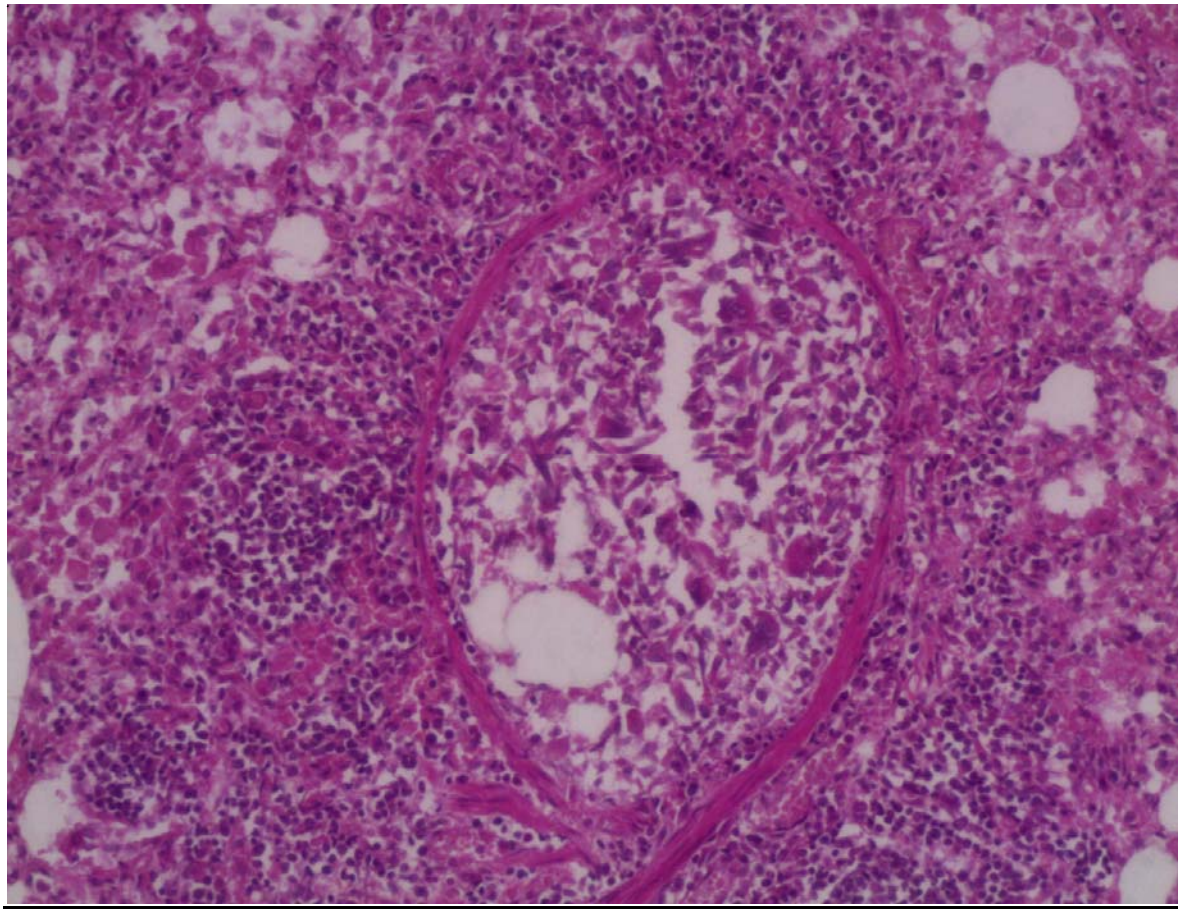
Photograph 2



The histopathology of viral type lower respiratory tract infection has been described in the literature. In this study, five sections, one from each lung lobe were examined in all cases in this cohort.

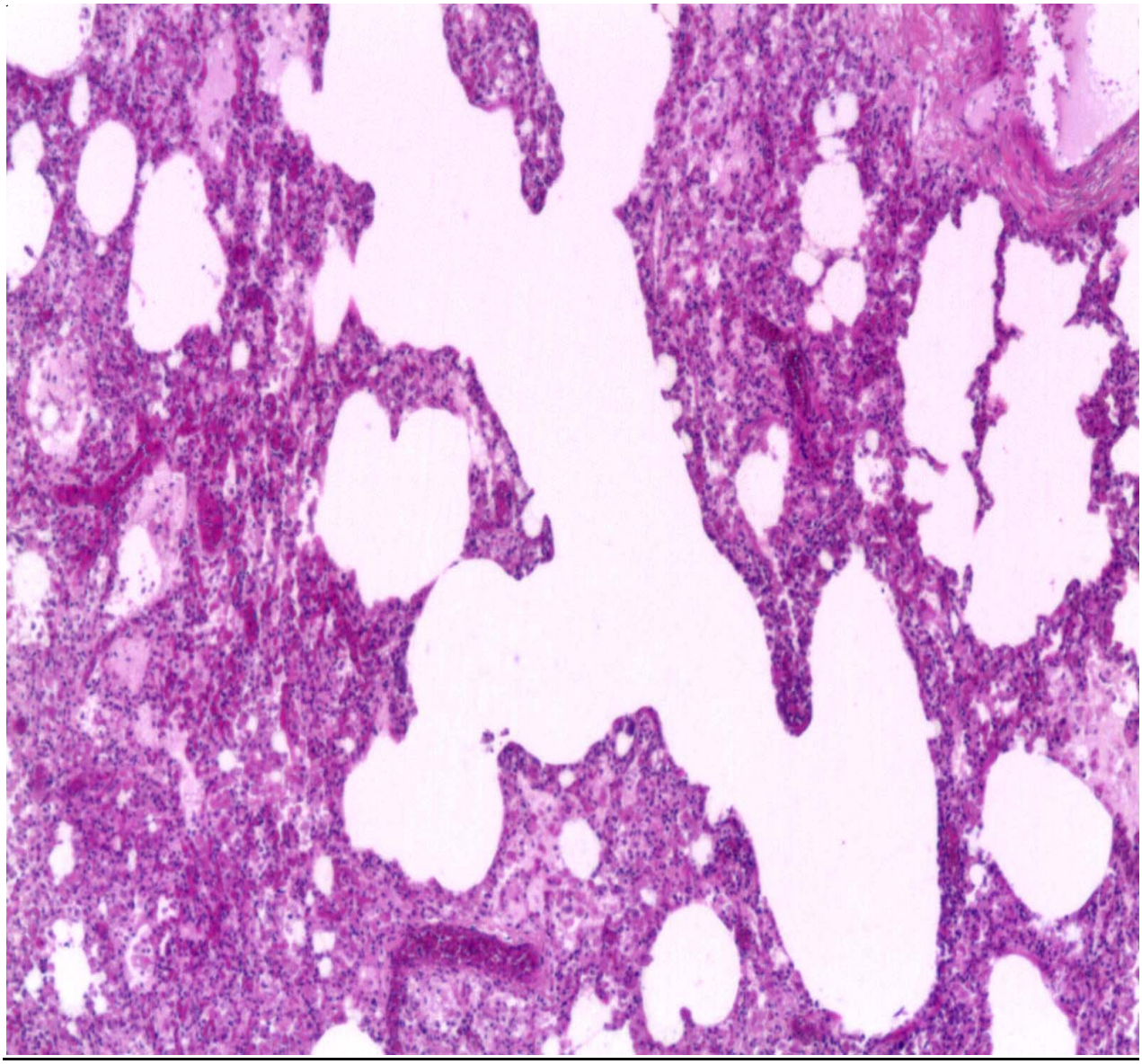
THE FOLLOWING PHOTOGRAPHS DEPICT THE PATHOLOGY ASSOCIATED WITH VIRAL TYPE LOWER RESPIRATORY TRACT INFECTION AS WAS EVIDENT IN THE COHORT

Photograph 1 taken from case no 6 showing intense bronchiolitis involving a terminal bronchiole. There is post-mortem shedding of the bronchiolar epithelium in the lumen.



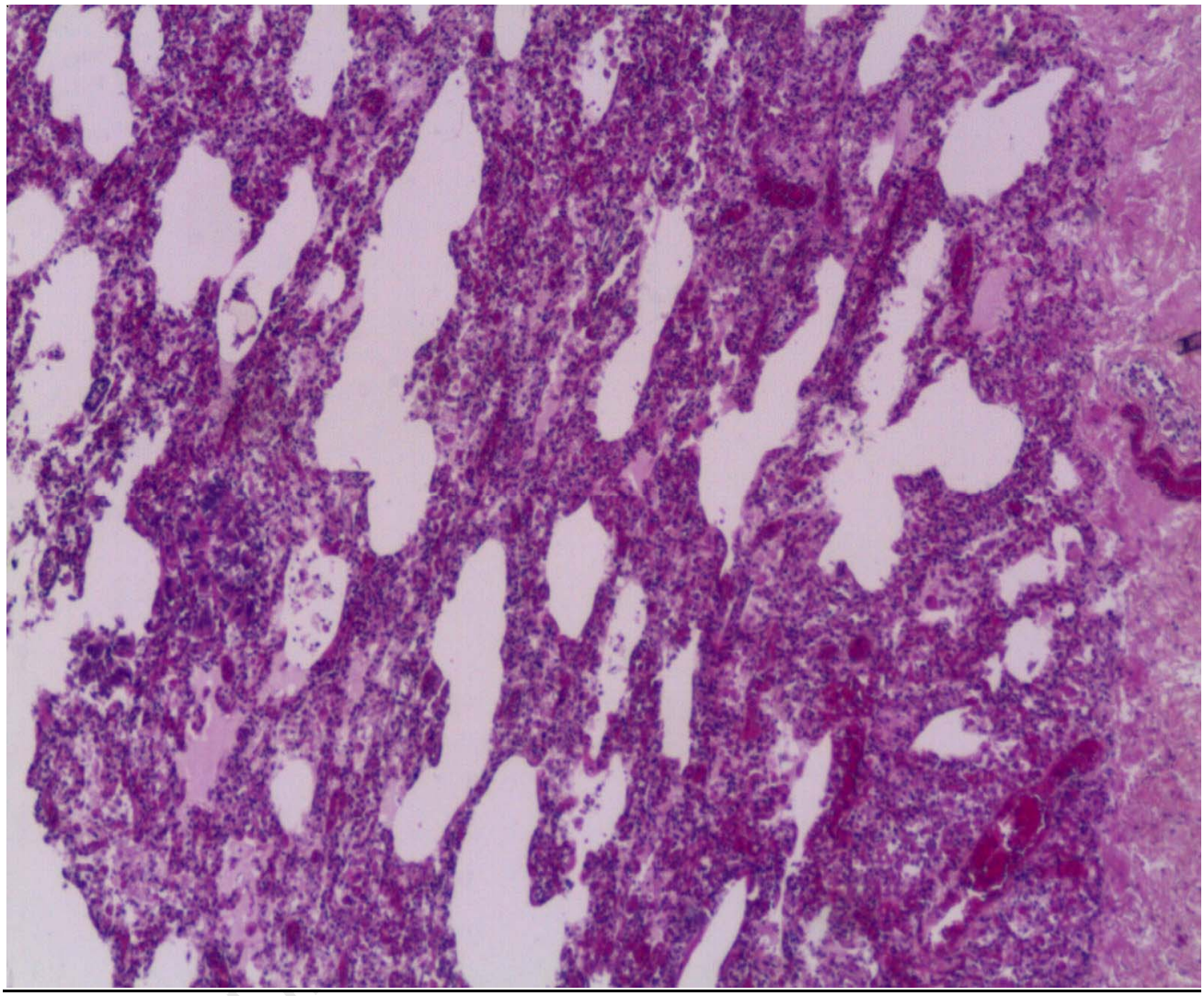
Mononuclear cells around a terminal bronchiole infiltrating smooth muscle

Photograph 2 taken from case no. 3 showing bronchiolitis involving respiratory bronchiole and alveolar ducts



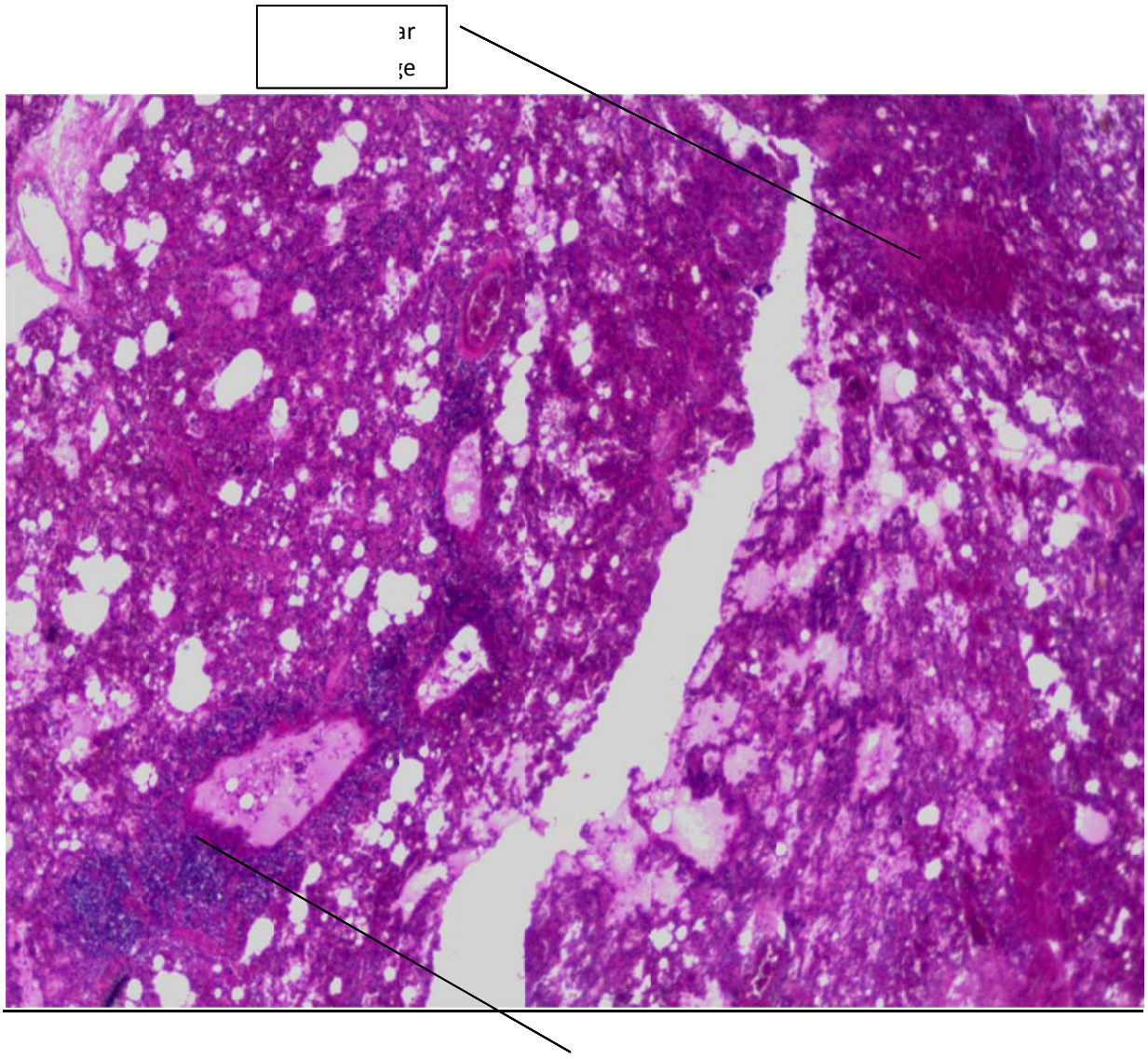
Bronchiolitis mononuclear cells
around a respiratory bronchiole

Photograph 3 taken from case no 8 showing interstitial reaction



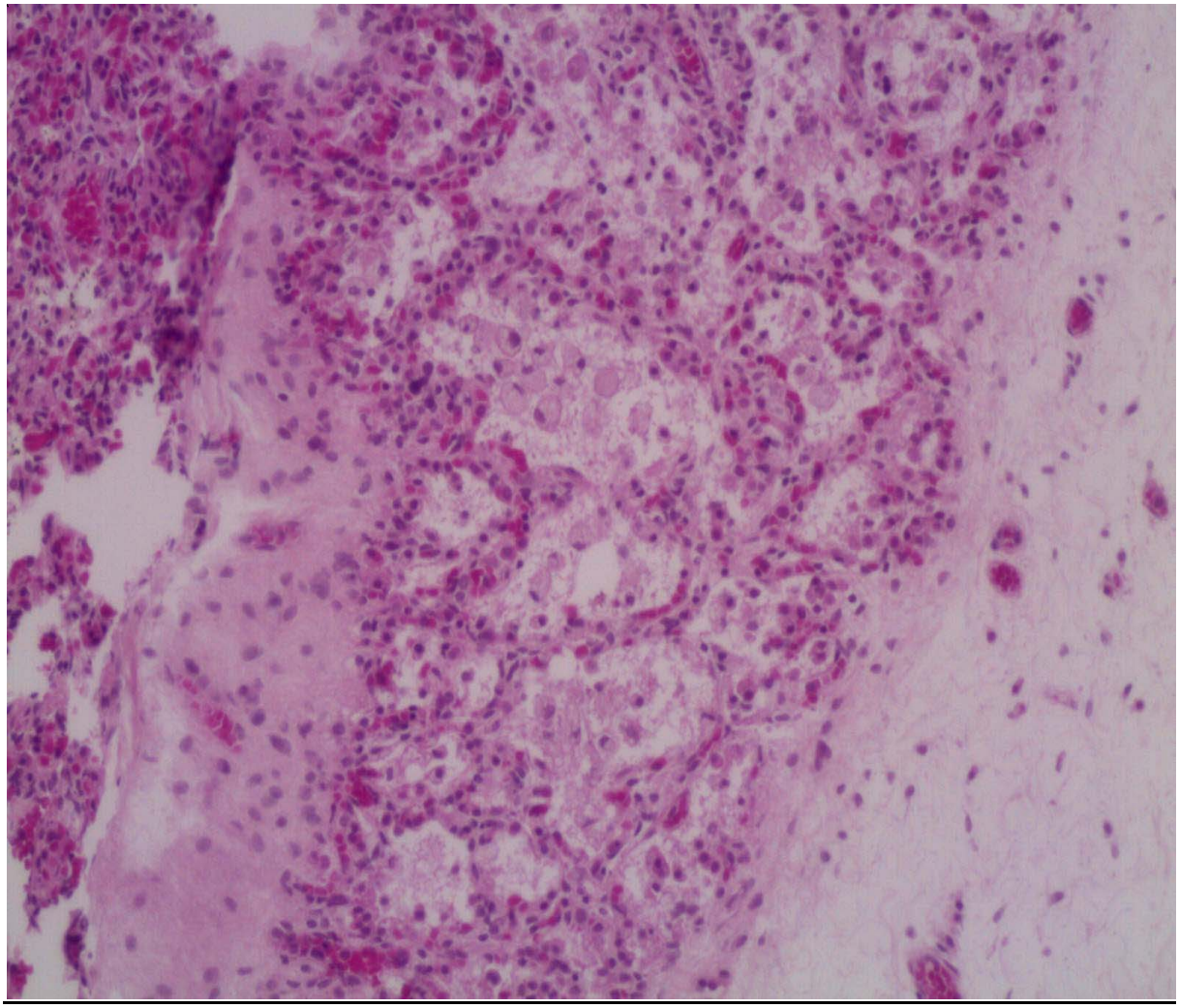
Interstitial reaction

Photograph 4 taken from case no 15 showing severe bronchiolitis and diffuse intra-alveolar haemorrhage



Photograph 5 taken from case no 3 showing aggregates of foamy macrophages associated in this section with minimal subpleural interstitial reaction, with alveolar space collapse in the top left corner of the picture.

Alveolar space collapse.

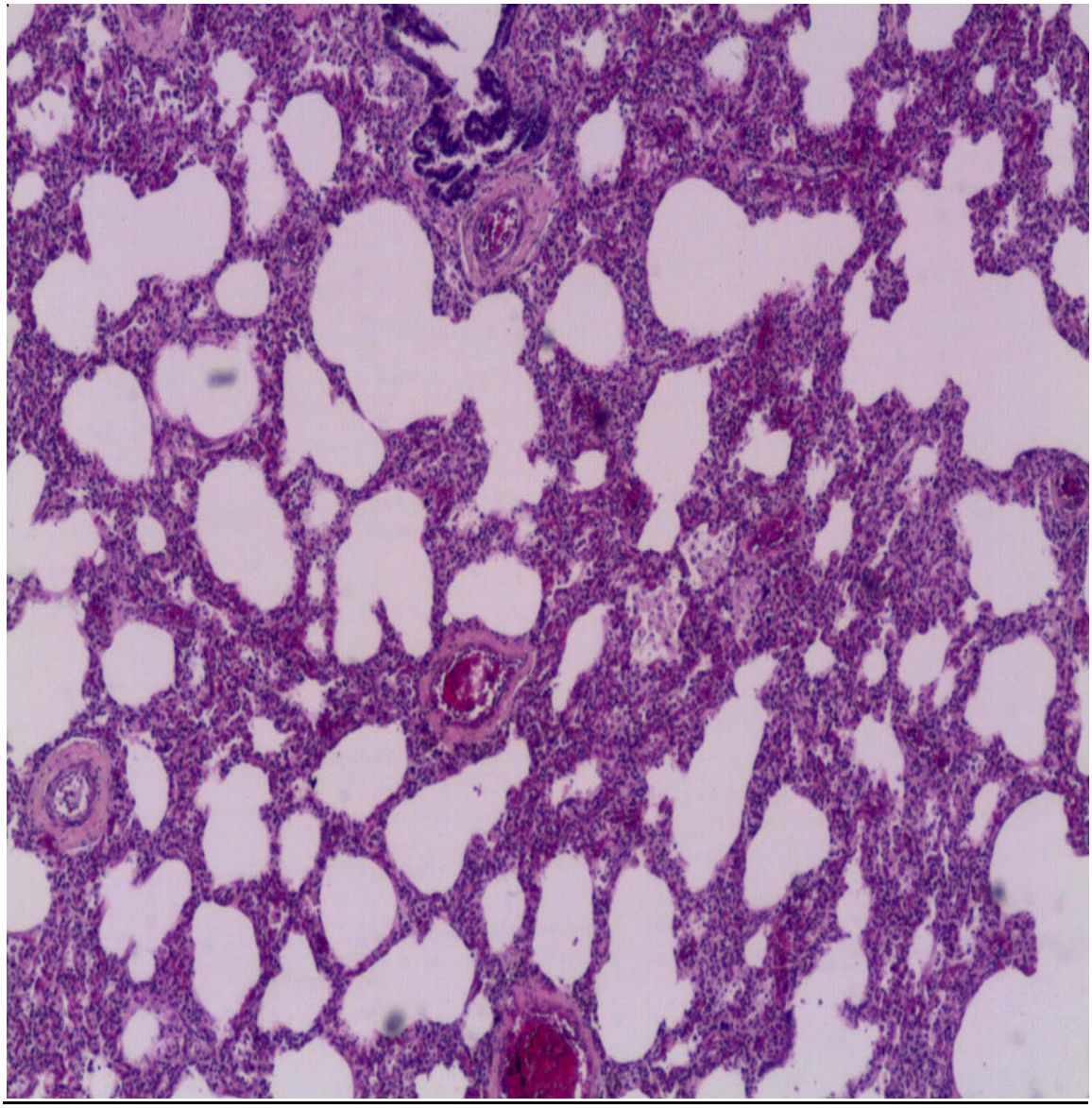


Aggregate of foamy macrophages

Photograph 6 taken from case 8 showing bronchiolitis and interstitial reaction and foamy macrophages.

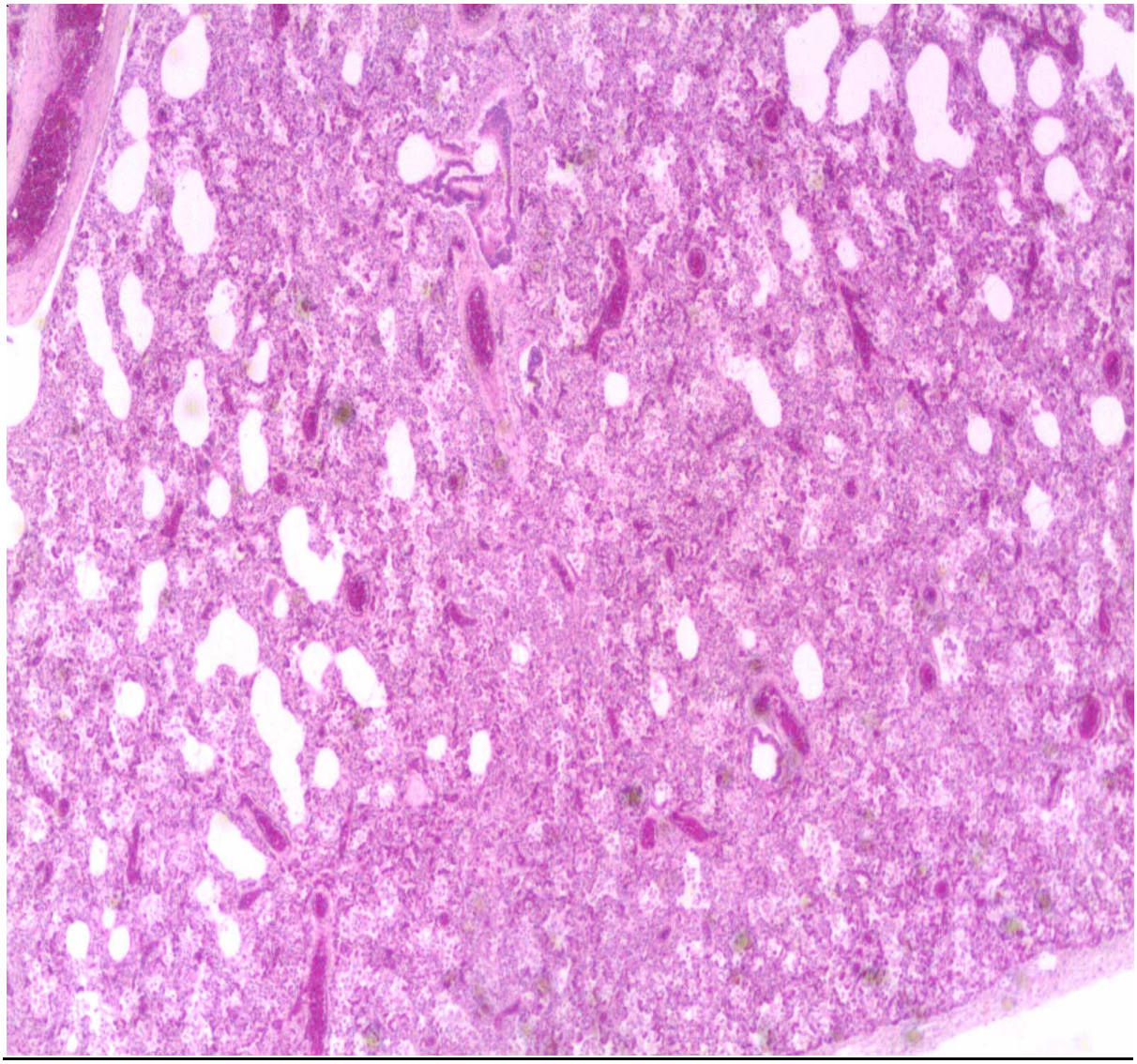
Bronchiolitis

Interstitial reaction



Foamy macrophages

Photograph 7 from case no 18 showing collapse of alveolar spaces and interstitial reaction.

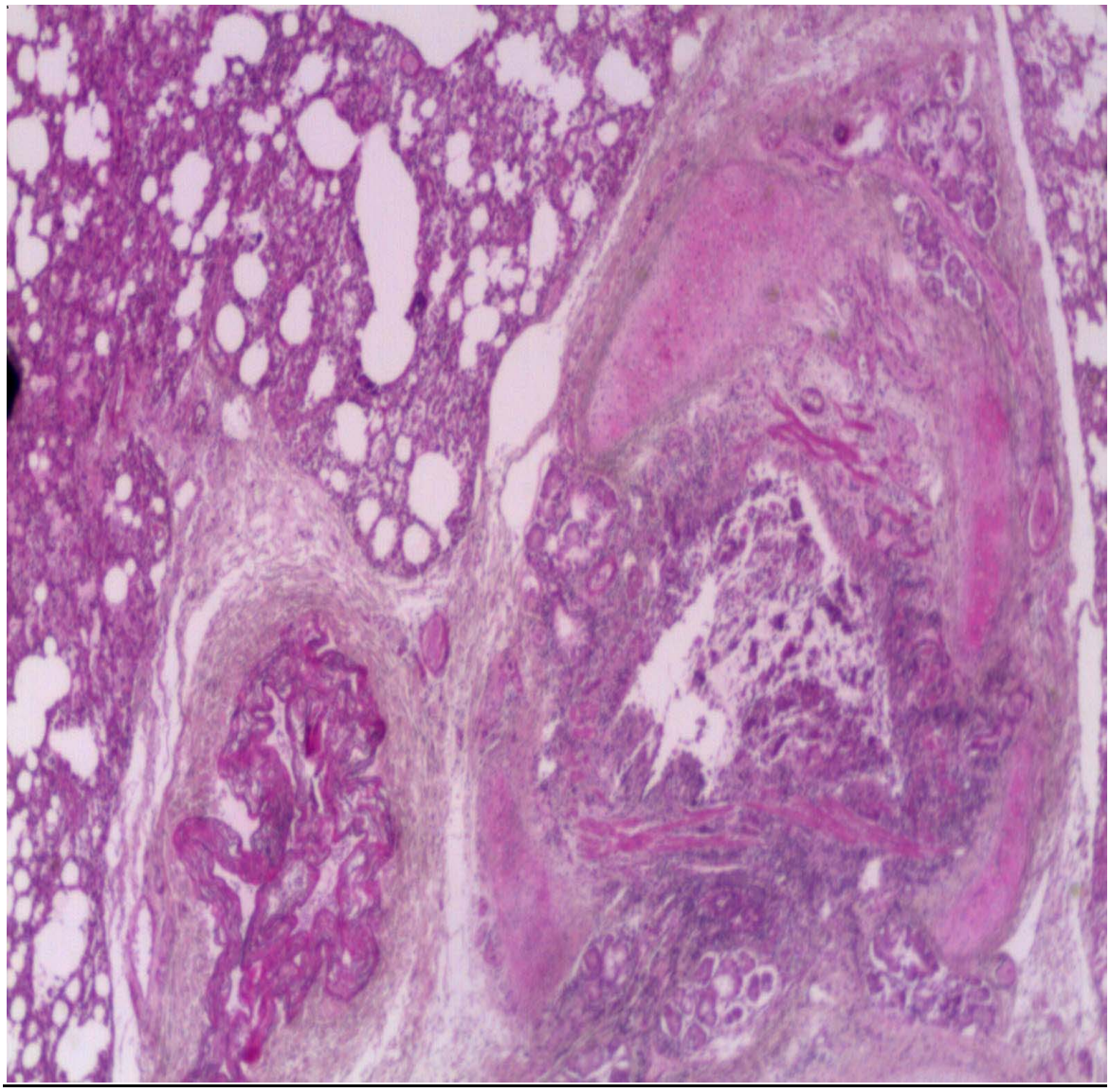


Collapse of alveolar spaces

Interstitial reaction

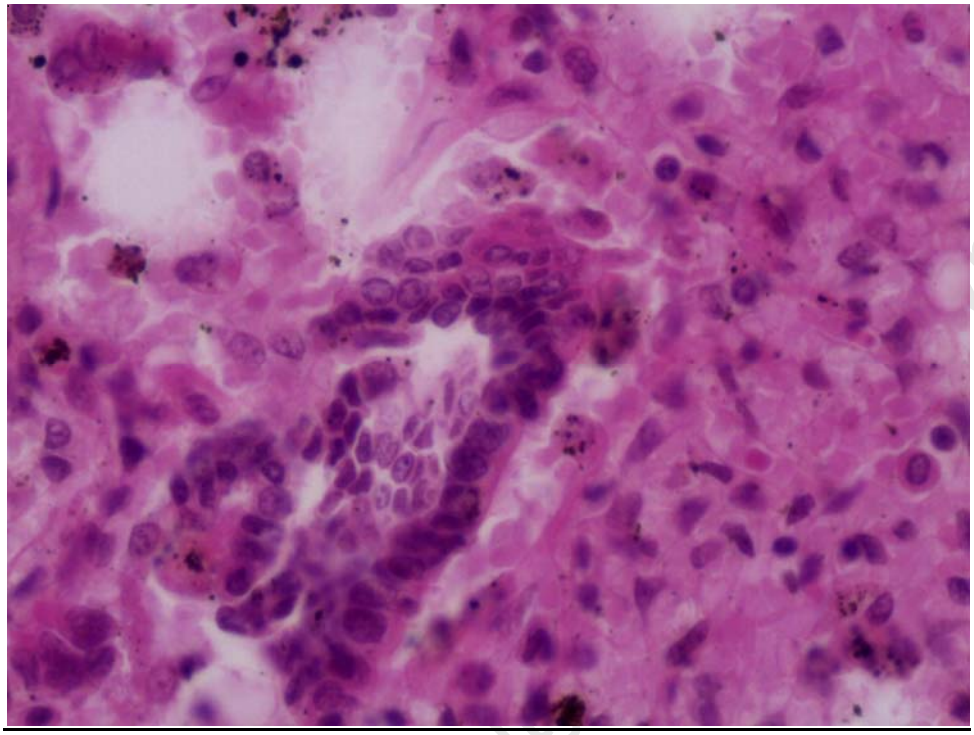
Photograph 8 from case no 1 showing severe bronchitis, associated collapse of alveolar spaces, interstitial reaction and bronchiolitis.

Collapse of alveolar spaces
around an area of bronchiolitis



Bronchitis: Mononuclear cell
infiltrate in the submucosa

Photograph 9 taken from case no 3 showing RSV syncytial formation



Syncitial formation

The lung histopathology of 6 of the 7 cases where death was attributed to viral lower respiratory tract infection (viral type), showed, in contrast to the normal lung histology and the controls, the following widespread/diffuse two pathologies consistently to be present in two or more lung sections:

- Bronchiolitis: this involving mainly the respiratory bronchioles and alveolar ducts
- Interstitial pneumonitis/reaction i.e. the interstitium being expanded by mononuclear cell infiltrate in the interstitium.

The following was present in varying degrees, being focal to diffuse in some lung sections

- pulmonary oedema
- collapse of alveolar spaces

Bronchitis was found to be mild in these cases.

In the 7th case of viral type lower respiratory tract infection, bronchitis was severe. The bronchiolitis and interstitial reaction pattern evident in the aforementioned 6 cases was not evident here. Instead, this pattern was present in a few patchy areas in the lung sections.

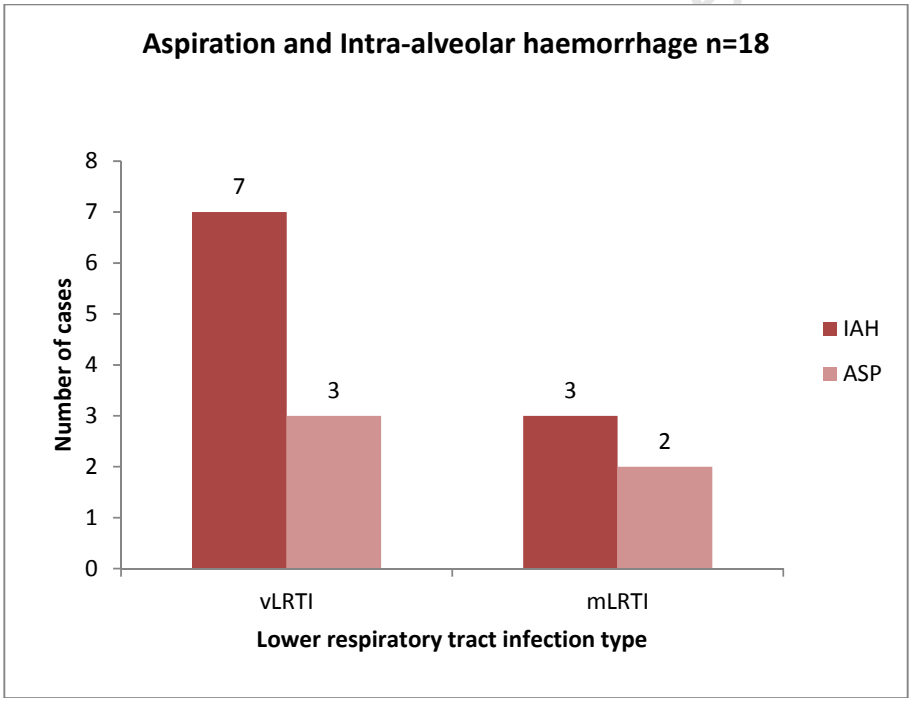
Where mixed/polmicrobial lower respiratory tract infection was present (6 cases, with reference to Annexure 7 these include cases 5, 9, 10, 11, 12 and 17) there was viral type lower respiratory tract infection and superimposed focal bronchopneumonia evident in the lung sections. The presence of viral type giant cells was not uniformly noted in the lung sections.

ASSOCIATED PATHOLOGY IN CASES DUE TO LOWER REPIRATORY TRACT INFECTION

Graph 5

The graph depicts intra-pulmonary haemorrhage to be evident in all of the seven (7) death cases due to viral type lower respiratory tract infection and in half of the six (6) cases due to polymicrobial infection. Aspiration of gastric content was present in both viral and polymicrobial lower respiratory tract infection but was not as common as intra-pulmonary haemorrhage.

The aspirated material was not associated with a foreign body giant cell response.



In 16 of the 18 cases, the thymus showed features of early involution which was reflected by a starry sky pattern. The thymus showed features of early involution in 6 of the death cases due to viral type lower respiratory tract infection. It showed atrophy in the 7th case.

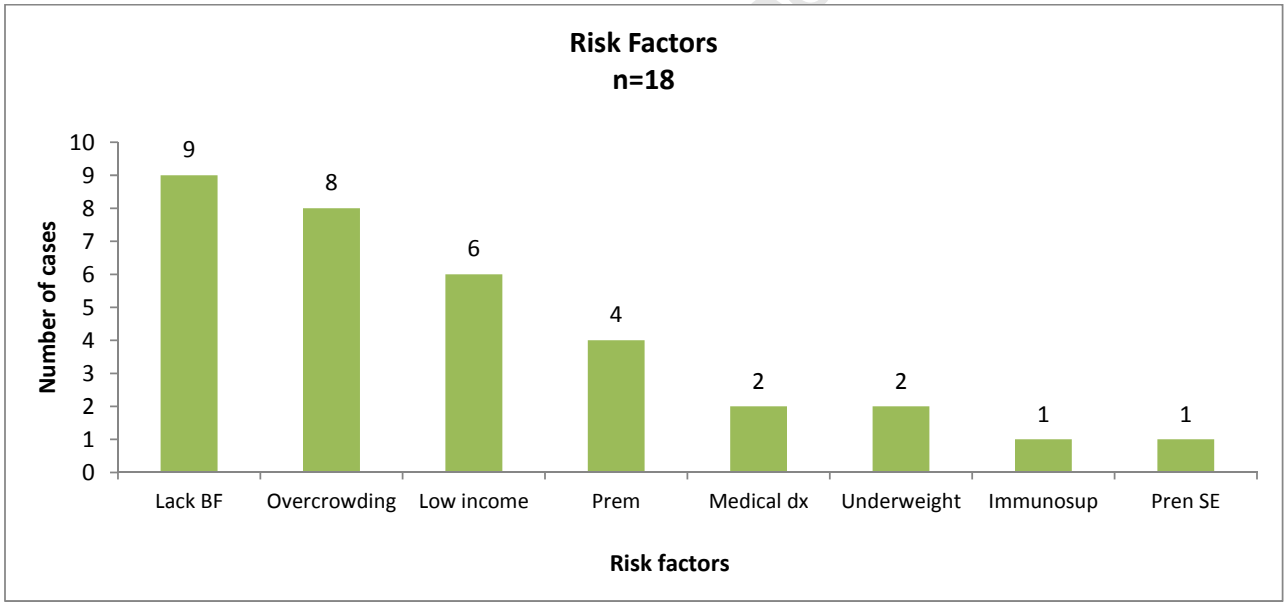
The thymus showed features of early involution in 5 of the 6 cases of deaths due to polymicrobial lower respiratory tract infection. It was not sampled in the other case.

Upper respiratory tract infection was present in only 2 of the 7 cases of viral type lower respiratory tract infection. In one case it was mild and the other severe. Of the 6 cases of polymicrobial type lower respiratory tract infection, the larynx was not sampled in two cases. Upper respiratory tract infection was present in 4 cases. 3 cases had mild infection whilst 1 had severe infection.

In 2 cases of lower respiratory tract infection both being of viral type, focal aggregates of foamy macrophages were evident.

Toxicology was performed on 17 of the cases in the cohort, all of which was negative. The case in which it was not performed, was one which involved congenital heart disease and lower respiratory tract infection, where the cause for death appeared obvious.

Graph 6
The graph below depicts the risk factors associated with lower respiratory tract infection, based on the data analysis of the SUDI Questionnaire in Annexure 1.



Lack of breast feeding and overcrowding (5 people or more in a small dwelling) were the found to be the most important risk factors associated with lower respiratory tract infection in this cohort. These accounted for 69.2% and 61.5% respectively of risk factors for lower respiratory tract infection. These risk factors were followed by low income (which was associated with overcrowding), prematurity and underlying chronic medical disease and underweight for age. The chronic medical disease cases involved 2 cases of congenital heart disease. Immunosuppression and tobacco smoke exposure were not common risk factors.

Eleven of the 13 cases of lower respiratory tract infection had more than one risk factor. The combination of lack of breast feeding and overcrowding featured in 5 of the 13 cases (38.5%) of lower respiratory tract infection. The 2 cases where only one risk factor was involved were cases of viral lower respiratory tract infection.

In 10 of the 13 cases of lower respiratory tract infection, no alcohol was used during the day or night of infant death. In three cases this information was not known. It had not been captured on the questionnaire.

Methamphetamine used by the caregiver on the day the infant's death in only one case. In this case, the death was due to polymicrobial lower respiratory tract infection.

Chapter 5

DISCUSSION

For the purposes of this study, the terms SUDI and its definition as proposed by Sidebottom [57] i.e. “the death of an infant which was not anticipated as a significant possibility 24 hours before death”, was used. The selection criteria for cases were;

a – infants who demonstrated no symptoms whatsoever prior to death (72.2%),

b – infants who were reported to have had minor symptoms by caregivers and who were considered to have been well (27.8%).

The sudden unexpected infant deaths were all explained deaths after thorough comprehensive post-mortems with ancillary investigations were performed. Most of the deaths were due to lower respiratory tract infection of both viral and mixed/polymicrobial type (72.2%). The other deaths were due to viral meningitis.

Histological examination of tissue in this study, in keeping with that conducted by Weber etal [63], is considered to be the most valuable investigation in determining cause of death. Microbiological examination of respiratory secretions proved to be of no value, yielding mixed growth in all cases. The main reason for this is considered to be post-mortem bacterial overgrowth, given that the post-mortem interval was on average 2.4 days. Although a bacterial pathogen known to cause pneumonia was isolated in two cases, given the associated mixed growth of bacterial organisms and the negative gram stain results on the lung sections, this is considered not to be of any significance. Virological culture yielded a positive result in 6 out of the 18 cases. The growth is not considered to be simply associated with a carrier state, given the histopathology of the cohort versus control cases. Viral detection was done by PCR in this study as detection by means of immunofluorescence (as determined in other studies) was found to be low [69].

Biochemistry on the vitreous in this cohort was not undertaken, given that on average the post-mortem interval was 2 days. A long post-mortem interval is known to adversely affect the value of the results.

A section from each lung lobe was examined histologically in the cohort. Controls used included cases in which death occurred in unnatural circumstances, and where there was no hospitalization involved. Age matched controls were not used in this study as these were difficult to find, however the cases selected involved children approximately 1 year or less.

In support of the diagnosis of viral lower respiratory tract infection, the histopathology in these cases showed obvious mononuclear inflammatory cell infiltrate in the lung

interstitium and around bronchioles. This was widespread within at least 2 lung sections. Although 2 of the control cases did show bronchiolitis and interstitial reaction it was not widespread within a lung section. Collapse of alveolar spaces and pulmonary oedema were prominent features in viral lower respiratory tract infection in comparison to the control cases. In only one case of viral lower respiratory tract infection, was the causative virus cultured i.e. RSV. The cases of polymicrobial lower respiratory tract infection showed the histopathological features of viral lower respiratory tract infection and bronchopneumonia.

In contrast to the RSV histopathology described by Johnson et al [47], in none of the lung sections pertaining to the aforementioned case of RSV lower respiratory tract infection, was there obstruction of the lumens of bronchi evident either by epithelial projections (syncytial giant cells), mucosal oedema, mucus, fibrin, or hyperplastic lymph nodes. The bronchitis evident in this case was associated with a mononuclear cell infiltrate rather than a neutrophilic infiltrate.

The collections of foamy, lipid laden intra-alveolar macrophages evident in 2 cases of viral type lower respiratory tract infection, are suggestive of endogenous lipid pneumonia. Lipid pneumonia is known to be due to the release of lipid from inflammation associated destruction of lung parenchyma distal to the site of obstruction. So despite there being no obvious bronchiole lumen obstruction in the lung sections it may be inferred, given this picture. Exogenous pneumonia in contrast does not have this microscopic appearance and shows lipid adjacent to airways with a foreign body giant cell reaction.

Aspiration of gastric content was present in both viral and polymicrobial lower respiratory tract infection but was not as common as intra-pulmonary haemorrhage.
The aspirated material was not associated with a foreign body giant cell response. From this it can be deduced that aspiration was either agonal or that passive regurgitation occurred in the post-mortem period.

All of the cases of viral lower respiratory tract infection and half of the cases of polymicrobial/mixed lower respiratory tract infection had intra-pulmonary haemorrhage of varying degrees. It is known to occur in association with bacterial pneumonia. In cases of viral lower respiratory tract infection, the intra-pulmonary haemorrhage is considered to be related to severity of the disease or diffuse alveolar damage [53]. Given the absence of bacterial pneumonia, sepsis, valvular heart disease, vasculitis, extensive hemosiderin laden macrophages, or evidence of a coagulopathy, and given that intra-pulmonary haemorrhage occurred in the control cases where death was asphyxial in nature, this haemorrhage is considered to be also in part hypoxia related.

Upper respiratory tract infection was not a common association with viral type lower respiratory tract infection being present in only 2 of the 7 cases (28.6%) compared to polymicrobial type lower respiratory tract infection where it was present in 4 of the 6 cases (66.7%).

In all but one of the cases of viral lower respiratory tract infection, the thymus histopathology was that of a starry sky pattern in keeping with acute stress reaction, which negates chronic infection. Symptomatology indicative of serious disease was absent in these cases. This could suggest:

a. The disease process was acute and there was no time for symptoms to manifest
b. The symptomatology was subtle and was therefore missed by the caregiver.

In the case where the thymus was atrophic, so attesting to chronic disease, it is probable that symptoms of disease were overlooked.

One of the limitations of this study is the sample size. The selection criteria for the cases included in the study, as well as the fact that the cases admitted to the SRFPL are from Cape Town western metropole only, is considered to have direct bearing on this.

The study period was selected to be during the rainy winter season in Cape Town where the incidence of pneumonia is known to increase [32]. In this cohort, lack of breastfeeding and overcrowding were found to be the most common amongst the known risk factors for lower respiratory tract infection. Overcrowding was an expected finding given that it occurs most commonly during the winter season during which this study was conducted. Eleven of the thirteen cases of lower respiratory tract infection had 2 risk factors. This appears to increase the risk for severity of the lower respiratory tract infection.

Prenatal and environmental cigarette smoke were not common risk factors. This was an unexpected finding and may be due the families of these infants being in the low income bracket and unable to afford cigarettes.

The usage of alcohol and drugs on the day or night of infant death was not found to be a significant risk factor associated with these death types.

This study may be biased as there were no SIDS (unexplained death cases) present. A possible reason for this is that some health care workers in the Cape Town western metropole may be completing death notification forms as “natural”, thereby bypassing the medicolegal autopsy. Population based studies are more likely to yield accurate data regarding SIDS prevalence and incidence than a small group study such as this.

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CONCLUSION AND RECOMMENDATIONS

CONCLUSION

This study has shown that both polymicrobial and viral type lower respiratory tract infection are the main causes for sudden unexpected infant death amongst cases admitted to the SRFPL in winter in Cape Town. Intra-pulmonary haemorrhage, although present in polymicrobial lower respiratory tract infection, was the most significant pathology associated with viral type lower respiratory tract infection, attesting to severe disease. Acute hypoxia was considered to be contributory.

Lower respiratory tract infection in this cohort was commonly associated with 2 of the known risk factors for this type of infection and is related to severity of disease. The usage of alcohol and drugs by the caregiver on the day or night of infant death was not a risk factor associated with these deaths.

The thymus histology which revealed features of a short duration stress reaction was in keeping with rapid, acute onset rather that chronic low grade infection, and this could account for the lack of symptomatology evident in majority of these death types.

RECOMMENDATIONS

The epidemiological risk factors for sudden death in this cohort are similar to those associated with lower respiratory tract infection, most of which are poverty based. The main epidemiological risk factors in this cohort were that of overcrowding and lack of breast feeding.

The prevalence of the disease would decrease if specific intervention strategies aimed at alleviating poverty are implemented.

a. Improving housing: this would decrease overcrowding [2, 21, 22] and so reduce the risk of bacterial and viral transmission. This could be achieved by governmental housing subsidies.
b. Providing running water to households in poor communities: this would promote hand washing and so decrease virus transmission by hand to hand contact [38,46].
c. Promoting breastfeeding and educating young mothers about its benefits [20].
d. Improving child nutrition in poor communities by way of outreach programs [29].
e. Providing better access to health facilities[29].

Education

a. Communities and community leaders should be educated about the prevalence and significance of lower respiratory tract infection being a major killer disease in childhood [1].
b. Children should be educated at school about the importance of hand washing and this should be re-enforced at clinics. Young mothers should be educated about maintaining clean surfaces. Municipalities could provide poor communities with soap for the purposes of hand washing.
c. Mothers with premature, low birth weight infants and medical disease should be educated about the dangers of lower respiratory tract infection. They should also be educated about the symptoms and signs of the disease.
d. Mothers should be educated about the association between prenatal and environmental smoke exposure and lower respiratory tract infection.
e. Educating health care workers at clinics about the signs of serious respiratory illness and its complications.[33]

Zinc supplementation

Given that elemental zinc has been shown to reduce viral replication, this could be added to infant feeds or/and given to children at schools [30].

Immunization

This should be promoted and at best maintained. In the Western Cape a study demonstrated that older children are less likely to receive vaccination compared to young children [23].

The infants who are at risk for severe lower respiratory tract infection should be targeted for vaccination i.e. those who are premature, who are not breastfed, who have medical disease, and who are of low birth weight. The vaccination should include not only

coverage for bacterial but also viral infection- RSV vaccine specifically, as this virus is the most important viral pathogen causing lower respiratory tract infection [34].

Given the complexity of the investigation into SUDI, it is recommended that these death cases be investigated by forensic pathologists who have expertise in paediatric pathology.

Research

a) Accurate data regarding the incidence and causes of sudden unexpected infant death in Cape Town and South Africa may be obtained if the entire population as opposed to a small cohort is studied.

b) Research into the role of prenatal Methamphetamine usage and sudden infant death should be undertaken, considering its prevalence on the Cape Flats.

c) Research should be also be directed at elucidating avoidable factors associated with natural child death cases at health care facilities so that services may be improved.

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APPENDICES

ANNEXURE 1. SUDI QUESTIONNAIRE

SALT RIVER MEDICOLEGAL LABORATORY

COMPLETE IF A BABY SHOULD SUDDENLY AND UNEXPECTEDLY DIE

INFORMATION PERTAINING TO THE CASE

RE WC11/_____

DATE _____

WHO GIVES THE HISTORY/INFORMATION IN THIS CASE eg mother/father/granny/grandpa/other relative (give details):_____

Infants full name: _____

Home Address: _____

Age of Baby _____ Date of birth: _____

Race: _____

Sex: _____

CIRCUMSTANCES OF DEATH

DETAILS ABOUT EVENTS BEFORE DEATH

_____

_____

_____

_____

_____

Who found the baby dead at scene: _____

When was the child last seen alive Date_____ Time:_____

When was the baby found dead Date_____ Time_____

Person (s) called to the scene: Name_____ Date _____
Time_____

Name_____ Date_____

Time_____

Police response Date_____ Time_____

Paramedic response Date_____ Time_____

When was death certified Date _____ Time_____

IF CHILD WAS TAKEN TO HOSPITAL

Name of hospital:_____

Date of arrival:_____ Time of arrival_____

Check please if the doctor's letter is available.

MEDICAL INFORMATION

Was the baby sick before it died? YES NO

If yes answer the following questions

	< 24 hours	24hrs to 2 weeks	> 2 weeks	Never
Did the child have a cold / runny nose?				
Was the child coughing?				
Did the child have diarrhoea (runny tummy)				
Was the child vomiting?				
Any fits / seizures?				
Did the child have a fever/showed increased sweating?				
Was the child listless (floppy)?				
Did the child turn blue?				

Did the child ever suddenly stop breathing? Yes No Unknown

Appetite change in past 48 hrs? Yes No Unknown

When was the baby's last vaccination?_____

Is the child known to be allergic to anything? YES No Unknown

If yes, to what?_____

Did the child come in contact with someone who is sick in the past two weeks? Yes No

Did the family visit another country prior to the death of the baby?

Yes NO

Did the baby sustain any injuries prior to death: Yes No

If yes

What happened_____

When did it happen_____

What did the care taker do about it _____

A. Please circle the correct one: Was the now deceased child taken to (1)**hospital** or (2)**clinic** or (3)**doctor** or (4)**pharmacy** for any of the above illness: Yes No

If Yes Date_____ Time_____

Medication (Names please) _____

B. Was the child **admitted to hospital** in the past week prior to death?

Yes No

If Yes For how long_____

Why? _____

_____

Discharge date_____

Condition of baby after discharge from hospital_____

_____

Medication after discharge from hospital (names please) _____

C. Was the child taken to a **traditional healer**: yes/no

If yes:

Date the child was taken to the healer:_____

What was given?_____

Ask for the medication so as to be given to the pathologist

Condition of the baby after going to the healer?_____

_____

Did the mother have a previous child that died suddenly? Yes No

If yes

How many died?_____

Why did they die?_____

At what age_____

Was a pm done?_____

Did the mother have a previous stillbirth? Yes No

HOUSEHOLD ENVIRONMENT

Does the baby live in a house shack other_____

Did the Forensic officer go to the dwelling? Yes No.

Was police called to the dwelling in the past? Yes No

If yes, Why?_____

Are there pets in the dwelling Yes No

If yes, what type_____

Is the dwelling damp? Yes No

Is there fungal growth in the dwelling? Yes No

Is there peeling paint in the dwelling? Yes No.

Where does the dwelling water supply come from?_____

Number of bedrooms in the dwelling_____

Are the odours/fumes in the dwelling_____

Number of adults in the house_____

Number of children in the dwelling_____

Total number of people in the dwelling?_____

Estimated monthly income?_____

Number of smokers in the house?_____

Are there mentally retarded/challenged people in the dwelling? Yes No

ABOUT THE MOTHER

Is the mother Married Single.

Is the mother employed Yes No

Age of the mother _____

What standard of schooling did she achieve_____

Was she on contraception before she fell pregnant? Yes No

Did she take iron and vitamin tablets during her pregnancy? Yes No

Did she receive antenatal care? Yes No

Did the mother have diabetes in pregnancy? Yes No

Did the mother have high blood pressure in pregnancy Yes No

Did the mother gain weight adequately in pregnancy Yes No.

Was the mother on any medication during pregnancy? Yes No

If yes, what medication_____

Was she depressed after the pregnancy? Yes No.

How many children does she have_____

How old are they_____

Are they healthy_____

Do the children have learning disability?_____

Do the living children have the same father as the deceased baby Yes No

Does she look after the baby Yes No

If not, who looks after the baby_____

Why is the mother unable to look after the baby?_____

Did the mother smoke during the pregnancy? Yes No

If yes, how many per day_____

Did the mother drink before she fell pregnant? Yes No

Did the mother drink during pregnancy? Yes No

If yes, how much did she drink

Every day	Now and again	Weekends
1 glass every day	Now and again	Weekends
> one glass every day	Now and again	Weekends
A bottle of alcohol every day	Now and again	Weekends
A papsak every day.	Now and again	Weekends

What did she drink? Beer Wine Papsak Brandy Other_____

Does she use drugs Yes No

If Yes, what drugs does she use?

TIK COCAINE HEROIN MANDRAX DAGGA OTHER_____

Does the mother smoke after the pregnancy? YES NO

Does the mother drink after the pregnancy? YES NO

Does the husband/partner drink? YES NO

Does the parents of the mother drink? YES NO

Does the mother know that smoking harms the unborn baby? YES NO

Does the mother know that alcohol harms the unborn baby? YES NO

ABOUT THE BABY

Where was the baby born?

Hospital Clinic Home Other_____

Name of the hospital/clinic_____

How was the baby born? Pleas tick

Normal vaginal delivery

Caesarian section

How much did the baby weight at birth_____

Was the baby Premature Full term Post-mature

If baby was premature, how premature was it?_____

Did the baby receive Kangaroo care? Yes No.

Did the mother carry the baby on her back Yes No

Was the child breast fed bottle fed

If bottle fed, name of the milk___________

Was boiling water used to make the bottle Yes No

What other food stuff (s) was used to feed the baby?____

Did the mother bring the clinic card? Yes No

If No, Why not ___________

Make Photocopy for the pathologist please.

>>

What did the baby wear when it died?

LIST CLOTHING____

Where (on what) was the baby placed to sleep: Please tick.

1. Bed on a pillow

   Bed without a pillow

2. Couch on a pillow

   Couch without pillow

3. Cot on a pillow

   Cot without a pillow

4. Floor on a pillow

   Floor without a pillow

5. Other_____

If placed on a bed/cot, what was the **mattress type**

Foam rubber Inner spring Other_____

Was the **mattress covered** with a blanket or sheet?

Yes NO

What was used to cover the baby

List items_____

Was the following in the room where the child slept to heat the room

Electric heater "Galley blik" Fire Other_____

Was the window in the room where the child slept on the day/night of death?

Open Closed

Does the mother or other people usually smoke in the same room where the baby slept?

Yes No

Did they or the mother smoke while they child slept on the night/day of death?

Yes No

Did the mother give the child medication on the day/night of death?

YES NO.

If yes, what medication, name please_____

Where was the baby found dead?

BED COUCH COT FLOOR OTHER_____

What position was the child placed when put to sleep?

Back Stomach Side Other_____

What position was the child found dead?

Back Stomach Side Other_____

Face position when the child **was found dead**: Please tick.

Unknown

To the left

To the right

Face down

Face up

Face and or chest squashed between any object(s)

when the child was found dead? Yes No Unknown.

If yes, details please

_____
_____
_____
_____

Was the nose and the mouth of the baby covered by anything e.g blankets, or anything else?

Yes No Unknown

Were there other items found in contact with the baby e.g pillow?_____

Did the baby use a Dummy

Yes No

Did the baby sleep in the same bed as the mother?

Yes No Not applicable

Did the baby sleep in her arms? Yes No Not applicable

Did the baby sleep on her chest? Yes No Not applicable.

Did the baby sleep with the mother on a couch?

YES NO Not applicable

How many people slept on the same bed as the baby at the time the baby died?_____

Was anyone found on top of the baby while in the bed?

Yes No

When was the baby last fed?

Date_____ Time_____

Did the mother use alcohol before going to bed with the baby on the night/day the baby was found dead?

Yes No

If yes, how much did she drink?_____

Did the mother use drugs before going to bed with the baby on the night/day the baby was found dead?

Yes No

If yes, what drugs?_____

COMMENTS TO PATHOLOGIST:

ITEMS RETAINED AT THE SCENE OR FROM THE MOTHER DURING INTERVIEW

I certify that the answers given herein were given to the best of my knowledge and that I did not withhold any relevant information.

oooOOOooo

1. I know and understand the contents of this declaration.

2. I have no objection to taking the prescribed oath.

3. I consider the prescribed oath binding on my conscience.

SALT RIVER

DATE:

SIGNATURE or THUMBPRINT OF DEPONENT

_____

NAME_____

I certify that the deponent has acknowledged the he/she knows and understands the contents of this declaration which was sworn to before medico-legal post-mortem examination and that the deponent's signature was placed thereon in my presence at SALT RIVER on
.....

.....

COMMISSIONER OF OATHS

FULL NAMES:
.....

DESIGNATION (RANK):
.....

BUSINESS ADDRESS:
.....

ANNEXURE 2

TABLE depicting the gender, race, age, risk factors

Cases	Gender	Race	Age	Over Crowding	Breast Fed	Nutrition	Medical Dx	Premature	Immunos upp	Prenatal SE	Environ SE
1	female	African	5m1w	7 people	No	Normal	No	No	No	No	No
2	male	African	2m2w	3 people	Yes	Normal	No	No	No	No	No
3	male	African	3w	5 people	No	Normal	No	No	No	No	No
4	male	Coloured	2m	2 people	No	Normal	No	No	No	yes	No
5	female	African	2m1w	7 people	No	Normal	No	No	No	No	No
6	female	African	2m1w	3people	Yes	Normal	No	No	Yes	No	No
7	male	African	2m	5people	Yes	Normal	No	6 months	No	No	No
8	male	Coloured	2w	2people	Yes	Normal	No	No	No	Yes	No
9	female	African	4m1w	8people	No	Normal	No	No	No	No	No
10	male	Coloured	4m	10people	No	Normal	No	No	No	unknown	No
11	male	African	1m3w	3people	No	Underweight	No	No	No	No	No
12	female	African	5m2w	6people	No	Underweight	Heart Dx Tri21	Yes	No	No	No
13	female	African	1m3w	7people	Breast & bottle	Normal	No	33 weeks	No	No	No
14	female	African	2m2w	2people	Yes	Normal	No	28 weeks	No	No	No
15	female	African	3m	2people	No	Normal	Heart Dx	6 months	No	No	No
16	male	Coloured	1m1w	4people	Breast & bottle	Normal	No	No	No	No	No
17	male	Coloured	1m2w	6people	Yes	Normal	No	No	No	No	No
18	male	African	1m2w	3people	No	Normal	No	34 weeks	No	No	No

ANNEXURE 3

TABLE depicting Microbiology and Virology results

Cases	CSF Culture Result	Blood Culture Results	Tracheal swab culture	Lung Virology
1	Specimen not analysed	Gram positive bacilli Gram negative bacilli	Neutrophils + Gram pos cocci +++ Gram neg cocci ++ Gram negative bacilli +++	Right lung PCR: pos adeno, RSV Left lung PCR neg
2	Cell count lymphocytes ++/cu mm Gram stain: bacteria gram pos in chains Culture: mixed growth, no meningeal pathogens	Positive Gram pos bacilli-large Organisms: Clostridium perfringens	Specimen not analysed	Right lung PCR: neg Left lung PCR: neg
3	Gram stain: gram neg bacilli ++ No classical meningeal pathogens	Positive Gram neg bacilli Gram pos bacilli Organisms: Enterobacter cloacae Corynebacterium species	Gram stain: neutrophils + Gram pos cocci + Gram neg cocci +++	Left lung PCR: neg Right lung PCR: neg
4	No growth	Positive Gram neg bacilli Gram pos bacilli, large Staphylococcus aureus coagulase neg Staphylococcus, anaerobic	Gram stain: neutrophils +, Gram pos cocci, Gram pos bacilli + Gram neg bacilli ++ Aerobic organisms : mixed growth (moderate)	Lung PCR enterovirus: pos Lung PCR respiratory virus:- neg
5	No growth	Gram neg bacilli Gram pos bacilli Organisms isolated: Escherichia coli Skin flora	Gram stain: neutrophils + Gram pos cocci ++ Gram, neg bacilli ++ Aerobic orgaisms: mixed growth	Lung PCR RSV and enterovirus: neg
6	No growth – insufficient to perform cell count	Positive Gram neg bacilli Gram pos cocci Organisms isolated: Klebsiella pneumoniae Coagulaae neg Staphylococcus	Gram stain: neutrophils + Gram pos cocci + Gram pos bacilli + Gram neg bacilli +++ Aerobic organisms: Klebsiella pneumoniae – abundant growth	Lung PCR respiratory virus: neg
7	No bacteria	Positive Gram pos cocci in clusters Organisms isolated: skin flora	Gram stain: neutrophils + Gram pos cocci + Gram pos bacilli + Aerobic organisms: mixed growth (abundant)	Lung PCR respiratory virus: neg
8	Mixed growth unsuitable for cell count No meningeal pathogens	Positive Gram pos cocci in clusters Organisms isolated: Staphyloccus aureus or	Gram stain: neutrophils ++ Gram pos bacilli + Aerobic organisms: Staphylococcus aureus (moderate)	Lung PCR respiratory virus: neg
9	No bacteria. No meningeal pathogens	Positive Gram pos cocci	Gram stain: neutrophils + Gram pos cocci +	Lung PCR respiratory virus: neg

		Organisms isolated: Staphlycoccus hominis	Gram neg bacilli +++ Aerobic organisms: mixed growth (abundant)	
10	Gram stain: lymphocytes were observed Erythrocytes Gram neg bacilli, Gram pos diplococci No meningeal pathogens	Positive Gram pos cocci in clusters Organisms isolated: Staphylococcus aureus Skin flora	Tracheal aspirate: gram stain – neutrophils not observed Epithelial cells not observed Mixed salivary organisms Aerobic organisms: Escherichia coli (moderate) Normal flora isolated (scanty)	Lung PCR respiratory virus: neg
11	Specimen not analysed	Organisms isolated: Escherichia coli Enterobacteria Coagulase neg Staphylococcus	Specimen not analysed	Lung PCR respiratory virus: Positive Para-influenza 1/2/3
12	Gram stain: no bacteria Culture: no growth	Neg after 5 days	Gram stain: neutrophils not observed Gram neg bacilli ++ Aerobic organisms: mixed growth (abundant)	Lung PCR respiratory virus: pos Metaphneumovirus: pos Respiratory virus: neg Swine flu A H1N1: neg
13	Gram stain: No bacteria Culture: No growth after 3 days	Negative after 5 days	Gram stain: neutrophils + Gram pos cocci + Aerobic organisms: Haemophilus Influenzea (scanty growth) Mixed growth (scanty)	Lung PCR respiratory virus: neg Swine flu A H1N1: neg
14	Gram stain: No bacteria Culture: No growth after 3 days	Negative after 5 days	Awaiting	Lung PCR respiratory virus: pos Metapneumovirus: pos
15	Not taken at autopsye	Not taken at autopsy	Not taken at autopsy	Not taken at autopsy
16	Gram stain: gram pos bacilli observed Unsuitable for cell count No meningeal pathogens	Pos, 15 hrs incubation Gram stain: grampus cocci in clusters & gram neg bacilli Culture: Acinetobacter baumannii & Staphylococcus saprophyticus	Gram stain: neutrophils + Gram pos cocci + Culture: aerobic organisms: mixed growth (scanty)	Blood PCR enterovirus: neg PCR respiratory virus: neg
17	No growth	Specimen not analysed	Moderate Staphlococcus aureus growth Normal flora isolated	Lung PCR Adeno and RSV pos
18	Specimen not analysed	Specimen not anaysed	Specimen not analysed	Lung PCR: Parainfluenza

Annexure 4

TABLE depicting the drug screen results

Cases	Drug screen
1	negative
2	negative
3	negative
4	negative
5	negative
6	negative
7	negative
8	negative
9	negative
10	negative
11	negative
12	negative
13	negative
14	negative
15	not done
16	negative
17	negative
18	negative

Annexure 5:

Table depicting the results on alcohol and drug usage on day and night of death

Cases	Illicit drug usage	Alcohol Usage
1	No	Unknown
2	No	No
3	No	Unknown
4	No	No
5	No	No
6	No	Unknown
7	No	No
8	No	No
9	No	No
10	Yes. Methamphetamine	No
11	No	No
12	No	No
13	No	No
14	No	No
15	No	No
16	No	No
17	No	No
18	No	No

ANNEXURE 6

TABLE depicting symptoms and post-mortem interval

CASES	SYMPTOMS	POST MORTEM INTERVAL NUMBER OF DAYS
1	Cough less than 24 hours	4
2	No	2
3	No	2
4	Minor fever, cough	3
5	Minor cough, runny nose	2
6	No	4
7	No	1
8	No	2
9	Minor cough	3
10	No	1
11	No	2
12	No	2
13	No	1
14	Cough less than 24 hours	4
15	No	3
16	No	5
17	No	1
18	No	1

ANNEXURE 7

TABLE depicting the causes of death

Cases	Histology	Cause of death	Virus cultured	Mixed/Polymicrobial LRTI
1	vLRTI Bronchitis predominantly IAH Aspiration gastric content Reactive thymus	vLRTI/bronchitis	RSV, Adenovirus	
2	v myocarditis Meningitis Reactive thymus	v myocarditis Meningitis	None	
3	vLRTI IAH Reactive thymus Foamy macrophages	vLRTI		
4	IPH Aspiration gastric content Reactive thymus Mild URTI	Aspiration gastric content	None)	
5	vLRTI Bronchopneumonia Reactive thymus Mild URTI	vLRTI with superimposed bronchopneumonia	None	sPolymicrobial growth Lung Gram stain: Negative
6	vLRTI IAH Reactive thymus	vLRTI	Non	
7	V meningitis Reactive thymus IAH Aspiration gastric content	V meningitis	None	
8	vLRTI IAH Reactive thymus Aspiration gastric content Foamy macrophages	vLRTI	None	
9	vLRTI bronchopneumonia IAH Aspiration gastric content Reactive thymus Severe URTI	vLRTI with superimposed bronchopneumonia	None	sPolymicrobial growth Lung Gram stain: Negative
10	vLRTI bronchopneumonia Reactive thymus IAH Aspiration gastric content Mild URTI	vLRTI with superimposed bronchopneumonia	None)	sPolymicrobial growth Lung Gram stain: Negative
11	vLRTI bronchopneumonia	vLRTI with superimposed bronchopneumonia	Parainfluenza Human metapneumovirus	sPolymicrobial growth Lung Gram stain: Negative

	Reactive thymus URT not sampled			
12	vLRTI IAH Aspiration gastric content bronchopneumonia congenital heart dx Reactive thymus Mild URTI	vLRTI with superimposed bronchopneumonia	Human metapneumovirus	sPolymicrobial growth Lung Gram stain: Negative
13	vLRTI Reactive thymus Mild URTI IAH Aspiration gastric content	vLRTI Mild URTI	None	
14	V meningitis Mild vLRTI IPH Aspiration gastric content	V meningitis	Human Metapneumovirus	
15	vLRTI congenital heart dx Atrophy of thymus IAH Aspiration gastric content	vLRTI	None	
16	v meningitis IAH Reactive thymus	v meningitis	None	
17	vLRTI bronchopneumonia IAH URT not sampled	vLRTI with superimposed bronchopneumonia	RSV, Adeno	sPolymicrobial growth Lung Gram stain: Negative
18	vLRTI IAH Severe URTI Reactive thymus	vLRTI Severe URTI	Parainfleuenza	