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A multidisciplinary investigation of a cluster of deaths on a paediatric intensive care unit

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Summary: During late December 1989 and early January 1990, a cluster of six unexplained deaths occurred on a paediatric intensive care unit (PICU) among children with congenital heart disease who had undergone cardiac surgical procedures. The children were all aged three years or less. In each case death was preceded by an unexpected increase in ventilatory pressure requirement followed by the development of a similar pulmonary shadowing on chest radiography. The radiological abnormality was felt to be consistent with a pneumonitis associated with some small airway disease. The clustering of these deaths, occurring in a similar unusual manner, was felt to constitute an outbreak warranting investigation. An Incident Committee was established to plan and manage a large multidisciplinary investigation during which the unit was temporarily closed. Following extensive investigation no bacterium, virus, fungus or other pathogen, toxic agent, or any other explanation for the cluster of deaths could be found. The possibility that the cluster occurred by chance remains although this was felt to be unlikely.

Keywords: Outbreak; investigation; nosocomial; multidisciplinary; paediatric intensive care; congenital heart disease.

Introduction

Four unexplained deaths occurred on the paediatric intensive care unit (PICU) of a central London post-graduate teaching hospital at the end of December 1989. The four children, aged between 2 weeks and 3 years, had congenital heart disease and all had been ventilated. The first two died on 22 December 1989 and the latter two on 31 December 1989. In each case death was preceded by a few days by similar pulmonary shadowing on chest radiography. A post-mortem examination on one baby had not revealed an infectious cause, and all microbiological investigations had failed to implicate any bacterium, fungus, virus or other pathogen.

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The initial investigation was carried out by an Infection Control Committee under the chairmanship of the Infection Control Doctor for the hospital, as recommended by the Department of Health and the Public Health Laboratory Service (PHLS) Hospital Infection Working Group in their guidelines on hospital infection control.¹

Immediate control measures included barrier nursing of all children on the PICU and a decision to admit no further children to the unit. Subsequently, all remaining children were transferred to another ward. On 5 January 1990 a fifth child developed a similar illness. The Infection Control Committee considered that the clustering of these cases constituted an outbreak and sought assistance in the investigation from the PHLS Communicable Disease Surveillance Centre (CDSC), and PHLS Division of Hospital Infection (DHI), and from the National Poisons Unit (NPU). An Incident Committee was established, chaired by the Director of Public Health of the local District Health Authority, which met the following morning, 6 January 1990, by which time two further children had died.

This paper describes the results of a multidisciplinary investigation and offers a model for the investigation of similar incidents.

Methods

The Incident Committee met regularly at the hospital; its terms of reference were:

1. to establish that an incident had occurred which required investigation;
2. to plan and manage the investigation;
3. to advise the hospital of the corrective action required;
4. to liaise with the press.

The following was devised as a working definition that best characterized the cases: a child requiring ventilation on the PICU who developed increased ventilatory pressure requirements followed, after 1–5 days, by otherwise unexplained bilateral diffuse pulmonary shadowing.

Hypotheses considered by the committee included: that the cluster of deaths was due to a microbiological agent; the cause was a prescribed drug, or a chemical administered either accidentally or deliberately; there was no common causal agent and that the incident represented the chance clustering of a number of severely ill children who died as a result of their congenital heart disease.

A review of the clinical record of each of the six cases, and of relevant medical, nursing and anaesthetic staff records was carried out to determine the detailed history of the final illness, to estimate the date on which the deterioration began which led to death in each child (the clinical onset), and to establish whether cases had in common any one of a wide variety of possible exposures (Table I).
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Table I. Key epidemiological information ascertained for each case and for staff

| Cases                              |
|------------------------------------|
| Date of onset of clinical deterioration |
| Date of death                      |
| Possible exposures to infective or toxic agents |
| Temporal relationship between these and all major clinical events |

| Staff                              |
|------------------------------------|
| Staff levels                       |
| Staff rotas                        |
| Changes and sickness absence       |
| Temporal relationships between these and clinical deterioration and death of cases |

The case notes of all children admitted to the PICU in the preceding month were reviewed to ascertain whether any other children had similar illnesses to the cases. All these children were followed up by checking outpatient notes and by direct contact with their parents by clinicians.

A note was placed in the Communicable Disease Report, which is circulated to microbiologists, public health physicians and other doctors in England and Wales, requesting that any similar cases be reported to CDSC. Informal contact with other large PICUs in the UK was also made. A facsimile transmission Toxic Alert call requesting information on possible aetiological agents, and on any other reported similar incidents, was made to Poisons Centres elsewhere in the UK and in Europe. The national news media carried reports of the incident.

An extensive internal microbiological, virological, haematological, biochemical and histopathological investigation of each of the six cases was undertaken along with a review of previous microbiological surveillance of PICU, adult intensive care unit (AICU) and the operating theatres. Further expert assistance in many aspects of the wide-ranging investigation was provided by many specialist bodies and organizations (see acknowledgements).

The DHI carried out further investigation of the environment in PICU and theatres, including full inspection and review of all monitoring arrangements (Table II).

The NPU established a Toxicology Working Group drawn from its medical, analytical and information staff. The Group considered all substances known to be present in PICU and routes of exposure which may have given rise to the illness observed. It also considered any substances reported in the literature to cause a similar illness but not known to be present on PICU. Samples were also obtained for toxicological examination (Table III).

The manufacturers of any drug, medical gas, or single use item or equipment on PICU, that was common to five or six of the cases were asked to provide quality control data. The intake to the compressed air supply was examined for possible sources of contamination.
Table II. Environmental investigation carried out in the paediatric intensive care unit (PICU) and operating theatres

| Policies              | Procedures                    | Equipment                        | Other              |
|-----------------------|-------------------------------|----------------------------------|--------------------|
| Sterilization         | Medical and nursing           | Ventilation systems              | Domestic           |
| Disinfection          | Drug administration           | Air conditioning systems         | Cleaning           |
| Isolation             | Dressings                     | Ventilators                      | Linen              |
| Visiting              | Record keeping                | Humidifiers                      |                    |
| Parental involvement  |                               | Sterilizers                      |                    |
| in care               |                               | Endotracheal tubes               |                    |
|                       |                               | Nasogastric tubes                |                    |
|                       |                               | Urinary catheters                |                    |
|                       |                               | Intravenous and arterial lines   |                    |

Table III. Samples obtained for toxicological analysis

- Blood, urine and endotracheal washings from cases where available
- Post-mortem specimens
- Cleaning materials and disinfectants used on PICU
- Water from the humidifiers
- Residues from ventilator tubes
- Discarded equipment in 'sharps' bins

Results

Five of the six children who died were female and all were aged 3 years or less (Table IV). All had pre-existing congenital heart disease and all except one had been admitted for cardiac surgery. Dates of admission ranged from 2 to 27 December 1989, and dates of death from 22 December 1989 to 6 January 1990. In each case a deterioration in clinical status occurred which was characterized by a requirement to increase ventilatory pressures to maintain satisfactory blood gas levels. This change was followed after 1-5 days by the appearance of otherwise unexplained diffuse bilateral pulmonary shadows on chest radiograph (Figure 1). The clinical change was usually accompanied by a change in white cell count characterized by a neutrophil leucocytosis but this was not felt to reflect necessarily an infective process. The ventilatory changes and radiographic appearances were felt to be consistent with a pneumonitis associated with some small airway disease.

Case histories

Case 1 was admitted with simple transposition of the great arteries. On arrival in the PICU, an umbilical arterial catheter (UAC) was inserted and a balloon atrial septostomy performed. Chest radiograph on the day of admission was normal. A day later she was extubated and her UAC was removed. Twenty-four hours later she developed necrotizing enterocolitis
Table IV. *Birth weight, sex, age at admission, underlying cardiac disease, and reason for admission of the six children*

| Case No | Birth weight (kg) | Sex | Age at admission | Underlying cardiac disease | Reason for admission |
|---------|------------------|-----|------------------|----------------------------|---------------------|
| 1       | 3.2              | F   | 1 day            | Transposition of great vessels | Balloon atrial septostomy |
| 2       | 3.2              | F   | 3 months         | Ventricular septal defect (VSD) and Ebstein's anomaly | Closure of VSD |
| 3       | NK               | F   | 3 years          | Vascular ring | Sleep apnoea for investigation |
| 4       | 3.3              | F   | 1 year           | Previous closure of VSD Multiple VSDs Double outlet right ventricle | Pulmonary artery banding |
| 5       | 2.9              | M   | 1 month          | Transposition, VSD and 'criss-cross' atroventricular connexion | Pulmonary artery banding |
| 6       | 4.0              | F   | 1 week           | Situs inversus, coarctation of the aorta, double outlet right ventricle subaortic stenosis, mitral stenosis | Balloon atrial septostomy Coarctation repair Pulmonary artery banding |

NK, not known.

(NEC) but had a normal chest radiograph prior to her clinical deterioration 9 days after admission. *Pseudomonas aeruginosa* was grown from an endotracheal aspirate, but the specimen had been obtained late in the illness, after the administration of antibiotics.

*Case 2* was admitted in clinical heart failure, with pulmonary hypertension and failure to thrive, for patch closure of her ventricular-septal defect (VSD). She was pyrexial on admission. Cultures of cerebrospinal fluid, urine and blood were sterile, and she responded quickly to treatment with broad-spectrum antibiotics. She underwent closure of her ventricular septal defect. The early post-operative period was complicated by the development of pulmonary hypertensive crises. Twelve days following admission she developed a pneumothorax and a chest drain was inserted. Clinical deterioration ensued a day later with increased ventilatory pressures and cardiac arrest. Four days after this a chest radiograph revealed bilateral infiltrates which persisted until her death. Scanty *Staphylococcus epidermidis* and *Candida albicans* were grown at various sites, but they were thought to be of minimal significance; a serum sample, thought to have been taken after a blood transfusion had been given, contained influenza A antibody at significant titres (including antibody to the then current community epidemic strain: A/England 427/88 H3N2 and to A/Shanghai 11/87 H3N2).

*Case 3* had undergone closure of a VSD in 1986. She was re-admitted for investigation of upper airways obstruction. On admission she had a febrile
convulsion for which no cause was found (blood culture, urine sample and throat swab yielded no growth), and rapidly recovered. A barium swallow was performed 2 days later and showed a vascular ring which was ligated and she was nursed with nasal continuous positive airway pressure post-operatively for 3 days. At this time a laryngobronchoscopy, carried out following collapse of her left lung, revealed copious purulent secretions in both main bronchi. *Haemophilus influenzae, Streptococcus pneumoniae* and respiratory syncytial virus (RSV) were found on culture of endotracheal aspirate and bronchial washings. She appeared to improve, but 3 days later she deteriorated and intermittent positive pressure ventilation became
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necessary. A chest radiograph later (after a further 2 days) showed bilateral infiltrates. Serological tests revealed a significant influenza A antibody titre but the specimen was thought to have been obtained after a blood transfusion had been given.

Case 4 was admitted for pulmonary artery banding following which she remained ventilator dependent with increased pulmonary blood flow. Rebanding of the pulmonary artery was carried out a week later but she continued to deteriorate and chest radiographic abnormalities ensued 3 days after this. Scanty C. albicans of dubious significance was isolated from an endotracheal tube tip and was also found in the post-mortem lung.

Case 5 was admitted at 1 month of age for pulmonary artery banding, having previously had a balloon atrial septostomy carried out. Following an initial banding operation he was ventilated until his death. He required a pulmonary artery rebanding but failed to improve post-operatively. Clinical deterioration was noted 3 days after the second procedure with repeated cardiac arrhythmias and increased ventilatory pressures. Two days after this his chest radiograph showed bilateral diffuse infiltration and he failed to respond to resuscitation. No significant pathogens were detected.

Case 6 was aged 1 week on admission for balloon septostomy, coarctation repair, and pulmonary artery banding. She was ventilated from the time of admission and tolerated a balloon septostomy well on the same day but developed a right pneumothorax following her cardiac surgery 3 days later. Clinical deterioration ensued after a further 7 days. C. albicans was found in upper respiratory tract swabs, but not in the post-mortem lung. Coliforms were also found in endotracheal and nasopharyngeal aspirates, but were unlikely to be of clinical significance.

Aspergillus species were not detected in any of the cases, and with the exception of the C. albicans mentioned, no other fungus was detected. Although RSV was detected in case number 3, it was not detected in any of the other cases. None of the cases were positive on antigen testing (or serology) for Legionella pneumophila, Pneumocystis carinii, Chlamydia species, or Mycoplasma pneumoniae.

Further microbiological tests, in addition to standard bacterial aerobic and anaerobic culture, were carried out for a wide variety of viral, fungal, bacterial and other pathogens, including those in Table V. Tests used, in addition to routine microbiology, included gene probes, direct antigen testing using monoclonal or polyclonal antibodies, serology, tissue culture including human embryonic lung tracheal organ culture, electron microscopy, and guinea pig inoculation. These did not reveal any further significant positive results.

Post-mortem findings
There were similar appearances in the three cases examined. Haemorrhagic pulmonary consolidation and evidence of epithelial necrosis were seen and
Table V. *Microbiological agents sought in available specimens from the six cases*

| Viral                              | Fungal              | Other                        |
|------------------------------------|---------------------|------------------------------|
| Adenovirus                         | Aspergillus fumigatus| Chlamydia psittaci           |
| Cytomegalovirus                    | Aspergillus terreus  | Coxiella burnetii            |
| Coronavirus                        | Aspergillus flavus  | Legionella pneumophila       |
| Coxsackie B virus                  | Aspergillus niger   | Mycoplasma pneumoniæ         |
| Epstein Barr virus                 | Aspergillus repens  |                              |
| ECHO virus                         | Candida albicans    |                              |
| Herpes simplex                     | Candida parapsilosis|                              |
| Human herpesvirus 6                | Micropolyspora faeni|                              |
| Influenza A and B                  | Pneumocystis carinii|                              |
| Measles                            | Thermoactinomyces vulgaris|                         |
| Mumps                              |                      |                              |
| Parainfluenza 1,2,3                |                      |                              |
| Parvovirus                         |                      |                              |
| Picornavirus                       |                      |                              |
| Polio                              |                      |                              |
| Rhinovirus                         |                      |                              |
| Respiratory syncytial virus        |                      |                              |
| Rubella                            |                      |                              |
| Varicella zoster                   |                      |                              |

* This list is not exhaustive as tests carried out included standard bacterial aerobic and anaerobic culture as well as culture of relevant samples in human embryonic cell lines, tracheal organ culture and guinea pigs.

the appearances were felt to be consistent with 'respiratory distress syndrome' which may be caused by viral pneumonia, chemical pneumonitis or cardio-pulmonary shock.

Pre-mortem and post-mortem samples from two cases were examined. No paraquat was found on examination of the blood or lung tissue, and 2,4,6-trichlorophenol (a constituent of the phenolic disinfectant) was not found on analysis of blood specimens. Pre- and post-mortem tests revealed only drugs which had been prescribed and their metabolites.

*Interval data*

The dates of admission to hospital and the occurrence of major clinical events for each case are shown in Figure 2. The interval from admission date to clinical onset ranged from 5 to 15 days (mean 10 days). The onset of clinical deterioration leading to death ('clinical onset') occurred between 3 and 10 days (mean 6 days) after the first episode of ventilation and ranged from 3 to 7 days (mean 5 days) after first operation in theatre (in the five who underwent this). The interval between clinical onset and death varied from 3 to 11 days (mean 6 days).

*Ventilation*

No single bed space in PICU was occupied by more than three of the cases. Five of six cases were ventilated with the same type of ventilator of which there were reported to be eight on PICU, while one case was ventilated only
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Figure 2. Chronological order of clinical events in the six children.

on another type. It was not possible to determine which specific machine had been used to ventilate each particular child, as ventilators were sometimes moved from one bed space to another. The timing of commencement of ventilation and the subsequent death in two cases, preceded the start of ventilation in two others; thus it was theoretically possible that two ventilators could have been used in four of the cases, but this could not be verified.

It was noted that six (5-litre) containers of a clear soluble phenolic disinfectant were present on PICU. A member of staff suggested that parts of the ventilator circuitry or humidifiers may, prior to their standard autoclaving between patients, have occasionally been soaked in a dilution of this substance. A ‘dummy run’ procedure was carried out after ventilator circuitry had been thus soaked and autoclaved, but the equipment could not function, and it was concluded that the cases could not have been exposed to residues of this substance.

Operations were carried out in three theatres, each of which had its own ventilator, and there was no evidence that a common exposure of cases to any one theatre prior to clinical onset of illness had occurred.

Staff details
Review of medical and nursing records revealed that no surgeon operated on more than three of the cases and several different anaesthetists had
responsibility for their pre-operative care. The same individuals were rarely rostered for duty during the 24 h preceding the clinical onset in more than one of the cases although senior nurses and junior medical staff were usually involved in the care of all such critically ill babies.

The sickness absence record for PICU nurses for the month of December 1989 and the first week of January 1990 showed that twenty of the 56 nurses (36%) took sick leave during this period, and in seven of these the term 'flu' was recorded.

Other unaffected children
Review of case notes of all children admitted to the PICU from 29 November 1989 until admissions ceased on 2 January 1990 revealed that 35 children (including the six cases) were admitted of whom 17 were female and 18 male; the ages ranged from one day to 15 years. Twenty-three were known to have had cardiac surgery and seven died on PICU. The seventh death in a very premature baby was caused by severe tracheal stenosis, and was clinically distinct from those in the cluster.

Ten of the remaining 27 babies admitted to PICU during December had a respiratory illness during the course of their inpatient stay but none appeared to have had an illness similar to that seen in the six who died. Two of these had RSV infection but no other significant pathogen was detected in the others. Subsequent follow-up of the 27 babies revealed that 17 were at home with no respiratory problems; three had minor respiratory illnesses only since discharge; two had chronic respiratory problems reported to be unrelated to their stay on the PICU; four had other unrelated problems, and one baby had died of hypoplastic heart disease.

Enquiries to other major centres did not reveal any other cases fulfilling the case definition.

Practices and procedures
It was not possible to observe usual working conditions, but on review by the DHI, all nursing procedures and practices in PICU and the theatres were considered satisfactory. Aspergillus fumigatus and Aspergillus niger were isolated from ducting in the ventilation system of AICU, PICU, and operating theatres and fumigation with formaldehyde was carried out following this.

Drugs or products administered
All six infants received the drugs dopamine, frusemide, vecuronium and gentamicin. Five of the six had received aminophylline, chloral hydrate, papaveretum (an opioid) and flucloxacillin, and morphine was given to three. Prostacycline and spironolactone had each been given to four of the infants. Quality control data from the manufacturers of these drugs and fluids was satisfactory as were the data relating to the manufacture and sterilization of single use items. Four of the cases were given parenteral feeds made up under
sterile conditions, and quality control checks were satisfactory. Benzyl alcohol preservative was not used in any intravenous solutions.

All six infants had one or more transfusions of blood or blood products prior to their clinical onset: three had whole blood transfusions, four received packed cells, all six were given intravenous albumin or plasma protein fraction (PPF) and two received plasma.

Discussion

During the previous 12 months there were 498 children admitted to the PICU of whom 53 (10.6%) died, including the five who died during December 1989. The number of deaths in any 1-week period ranged from none to four and averaged just under one per week and the deaths were distributed approximately randomly. The possibility therefore exists that this cluster occurred by chance alone and is explained by the coincidence of a number of unusually sick children on the unit in the holiday season. A clinical review of the cases in the cluster was carried out, after the initial stages of the investigation had been completed, and it was concluded that the first two cases did not have the florid radiographic shadowing seen in the other cases, and may not have been part of the cluster of apparently similar cases.

The likelihood that four deaths should occur in the unit in a 2–3 week period as a result of chance alone was considered statistically and was thought not to be a significant departure from the historical pattern. However, the striking feature about this cluster of cases was the similarity of the mode of death in at least four of the cases; in the judgement of the hospital staff on the Incident Committee, deaths in this manner were not seen more than once or twice a year. The clustering of cases, whether four or six in number, was therefore felt to be strongly suggestive of a common causal agent, and the Incident Committee agreed that every effort should be made to identify it.

The condition observed was thought by the clinicians and histopathologist to resemble adult respiratory distress syndrome (ARDS), which is not common in children but has been reported as a post-operative complication of cardiac surgery associated with high mortality in children.3

No respiratory pathogen (viral, bacterial or fungal) was found to be common to the cases. Although Aspergillus species and other fungi have been reported as the cause of respiratory illness in an intensive care setting,4,5 there was no clinical or laboratory evidence to suggest a fungal cause for this cluster of cases. One of the cases, and two other children on the PICU at the same time, had evidence of RSV infection. Viruses including RSV have been reported to cause outbreaks of respiratory illness of increased severity among infants with underlying cardiorespiratory disease.6-10

Both RSV infection and influenza A infection had increased to epidemic levels in the community in this country at the time of the incident.11
Outbreaks of influenza infections in neonatal intensive care units at the time of community outbreaks have been reported in the USA\(^7,12\) and nosocomially transmitted viral infections have also been associated with greater severity of symptoms in young infants with underlying cardiorespiratory disease.\(^2\) However, with the exception of the three-year-old case, there was no evidence of either of these infections in the cases involved. The infants affected in this cluster had clinical features not unlike those observed in the influenza A outbreaks described, including bilateral pulmonary infiltrates on chest radiography and a leucocytosis.\(^7,12\) Clinical features were less like those in RSV infection.\(^13\) The possibility remains that a viral illness among the staff members could have been passed to the children in the unit, but the negative results of the extensive microbiological studies make this unlikely. The sensitivity of the direct fluorescence tests used to detect these infections is high and it is unlikely that infection present at the time was missed.\(^13\) The results of serological tests however could not be relied upon: most of the cases had received blood or blood products and the tests do not discriminate between infant and maternal antibody. Furthermore the immunological response to infection in this group is unclear.

No common factor was identified in the epidemiological investigation that linked the cases and distinguished them from other children on the unit. Nor was any common time interval found that might link the onset of illness in the cases to any major clinical procedure.

Although all six cases received blood or blood products prior to the onset of their deterioration, it was felt unlikely that these events were associated because the blood products given to the six cases came from different donors or from large batches which were widely distributed and were not reported to have caused problems elsewhere.

Outbreaks of respiratory illness in neonatal units associated with medication errors have been reported.\(^14,15\) In addition, in the USA, an outbreak of cardiorespiratory deaths associated with digoxin toxicity was thought to have been related to the deliberate administration of the drug by a member of staff\(^16\) and in a further cluster of deaths due to cardio-pulmonary arrests in the USA, an epidemiological link was found with the presence of a particular staff member.\(^17\) No evidence was found in this investigation to link the deaths to the presence of any particular member of staff.

Respiratory distress syndrome in children has been reported following inhalation of hydrocarbon gas\(^3\) and contamination of gas supplies has been known to occur.\(^18\) Inhaled chemicals or air at high temperature may give rise to respiratory difficulty in ventilated neonates.\(^19\) However, although two ventilators could have been common to four of the cases in PICU there was no evidence that air at raised temperature or any noxious agent could have caused the illness. Furthermore, medical gases were reported within normal parameters.
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Opioids such as heroin have been reported to cause a similar clinical picture but although papaveretum was given to five of the six cases, and morphine to three, these drugs are widely used in the PICU and were judged unlikely to have given rise to the illnesses observed in these children.

Ultimately, it was not possible to exclude a toxicological cause for this cluster of cases, as it was only possible to analyse the available specimens for a small number of likely agents. Specimens have been held in reserve so that analysis for other toxic substances can take place should a theory about any other aetiological agent emerge.

This unexpected cluster of deaths, the considerable press interest, and the intensive nature of the investigation, temporarily affected staff morale at the hospital. However, the Incident Committee was led by an experienced chairman who facilitated frank, open discussion between the members of the large multidisciplinary team, and clear lines of communication existed between members of the Incident Committee and staff members at the hospital. Those most closely involved were briefed regularly on the state of progress of the investigations. All staff co-operated fully in the investigation, and were supported by the hospital management.

In conclusion, no explanation for the cluster of deaths was found, but the investigation did exclude many possible and preventable causes. However, the possibility that this cluster occurred by chance cannot be excluded. Although the standards of care on the PICU were considered to be very high, and although no infective cause was demonstrated, a thorough cleaning, disinfection and redecoration was subsequently carried out. Ultimately, the decision to re-open PICU was taken on the grounds that no scientific evidence existed to warrant keeping it closed. This recommendation was endorsed by a small group of independent experts who were invited by the Committee to review the investigation. The Westminster Coroner held inquests into the cause of death of the last two cases. In both cases a verdict of death by natural causes was recorded.

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