

Predictive clinicopathological features derived from systematic autopsy examination of patients who died with A/H1N1 influenza infection in the UK 2009–10 pandemic

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Declared competing interests of authors: none



Published December 2010

DOI: 10.3310/hta14550-02

This report should be referenced as follows:

Lucas S. Predictive clinicopathological features derived from systematic autopsy examination of patients who died with A/H1N1 influenza infection in the UK 2009–10 pandemic. *Health Technol Assess* 2010;**14**(55):83–114.

Health Technology Assessment is indexed and abstracted in *Index Medicus/MEDLINE*, *Excerpta Medica/EMBASE*, *Science Citation Index Expanded (SciSearch®)* and *Current Contents®/Clinical Medicine*.



Abstract

Predictive clinicopathological features derived from systematic autopsy examination of patients who died with A/H1N1 influenza infection in the UK 2009–10 pandemic

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Background: From April 2009 to January 2010, the pandemic of A/H1N1 influenza affected the UK. There were > 30,000 infections and 457 deaths (all ages). Reports from other countries had indicated that certain comorbidities were associated with a higher risk of death from H1N1 infection, and there was a need to identify these factors in the UK population as knowledge of them could lead to improved treatment in the current epidemic and reduced mortality in future epidemics.

Objectives: To gather all the available clinical pathology information from autopsies performed on patients dying with known or suspected influenza A/H1N1 infection, across the UK. To evaluate comorbidities present in these deceased patients; correlate them with the H1N1-related pathology and treatment-associated pathology, determine their relative contributions and estimate the significant features associated with death.

Methods: To obtain the autopsy reports, standard request letters were sent by e-mail to all histopathologists in the UK on the Royal College of Pathologists list, all the coroners' jurisdictions in England, Wales and Northern Ireland, and to procurators fiscal in Scotland. The letters asked for autopsy reports of the autopsied deceased who included: those with H1N1 infection, *proven* before or after death, *and* those in whom swine flu was unproven but most likely to have been present; those in whom H1N1 was a minor pathology, as well as those in whom it was the immediate cause of death; those whose cause of death mentioned 'swine flu', 'swine influenza' or 'H1N1 infection'; and those of any age from infancy to old age.

Results: Sixty-eight autopsy reports were received: 19 children (0–15 years) and 49 adults (16+ years). All

but two autopsies were medico-legal, and only two (3% of the total) were consented. This sample thus represents 15% of the known 457 deaths from H1N1. Median age for children at death was 6 years, for adults it was 41 years. Deaths in children were associated with congenital diseases (47%, 9/19), particularly of the heart and central nervous system. The autopsied children were not obese. Death in adults were associated with pregnancy (three cases in the study, but nationally 12/457 H1N1-associated deaths were noted), obesity (50% of adults had a body mass index $\geq 30 \text{ kg/m}^2$) and chronic respiratory disease (12%, 6/49 adults). Diabetes did not emerge as a risk factor for death, but learning difficulties did. Nearly all the deaths (94%, 64/68) were a consequence of H1N1 infection in the respiratory tract. In more than one-third (41%, 28/68) of the deaths, bacterial secondary infection was the significant complication; the pneumococcus was the most common agent identified (25%, 7/28).

Limitations: This review is an incomplete medical study of what happened during the epidemic, and the small sample number (68 reports from 457 deaths) limits further speculation. We have no true measure of whether the cases selected for autopsy are representative of the total deaths in terms of pathology and comorbidities.

Conclusions: The major comorbidities associated with death from H1N1 infection were obesity, chronic respiratory disease and pregnancy. Young age at death was confirmed. Congenital disease in children and learning difficulties in adults were also important, but diabetes was not. This methodology of gathering data for research has potential for use in other public health questions, but is dependent on the co-operation of the medico-legal services. These results reinforce the need to enquire further into the pathogenesis of severe and

fatal H1N1 disease, and the circumstances of clinical presentation and rapid evaluation in a time of epidemic influenza.

Funding: The National Institute for Health Research Health Technology Assessment programme.



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List of abbreviations

AEFI	adverse effects following immunisation	CSEW	Coroner Society of England and Wales
ALI	acute lung injury	HIV	human immunodeficiency virus
BMI	body mass index	HPA	Health Protection Agency
CMACE	Centre for Maternal and Child Enquiries	NCEPOD	National Confidential Enquiry into Patient Outcome and Death
CNS	central nervous system	NRES	National Research Ethics Service
COPFS	Crown Office and Procurator Fiscal Service	RCPath	Royal College of Pathologists

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.



Executive summary

Background

From April 2009 to January 2010, the pandemic of A/H1N1 influenza affected the UK. There were > 30,000 infections and 457 deaths (all ages). Reports from other countries had indicated that certain comorbidities (young age, asthma, pregnancy, diabetes, obesity) were associated with a higher risk of death from H1N1 infection, and there was a need to identify these factors in the UK population as knowledge of them could lead to improved treatment in the current epidemic and reduced mortality in future epidemics. In addition to clinical observation research in life, examination of autopsy data would provide information on the important comorbidities.

Objectives

- To gather all the available clinical pathology information from autopsies performed on patients – adults and children – dying with known or suspected influenza A/H1N1 infection, across the UK.
- To evaluate comorbidities present in these deceased patients; correlate them with the H1N1-related pathology and treatment-associated pathology, determine their relative contributions and estimate the significant features associated with death.

Methods

To obtain the autopsy reports, which would comprise the results of both medico-legal autopsies and hospital/consented autopsies, help was obtained from the Royal College of Pathologists (RCPath), the Coroner Society of England and Wales, the Crown Office and Procurator Fiscal Service and the Centre for Maternal and Child Enquiries.

Standard request letters were sent by e-mail to all histopathologists in the UK on the RCPath list, all the coroners' jurisdictions in England, Wales and Northern Ireland, and to procurators fiscal in Scotland. The letters asked for autopsy reports

with the following case definitions of the autopsied deceased:

- From pathologists:
 - those with H1N1 infection, *proven* before or after death, *and* those in whom swine flu was unproven but most likely to have been present
 - those in whom H1N1 was a minor pathology, as well as those in whom it was the immediate cause of death.
- From coroners and procurators fiscal:
 - mention of '*swine flu*', '*swine influenza*' or '*H1N1 infection*' in any part of the cause of death, i.e. in Part 1 *or* in Part 2 of the cause of death statement
 - any age from infancy to old age.

Results

Sixty-eight autopsy reports were received: 19 children (0–15 years) and 49 adults (16+ years). All but two autopsies were medico-legal, and only two (3% of the total) were consented. This sample thus represents 15% of the known 457 deaths from H1N1.

The total number of autopsied H1N1-associated deaths was not identified. The information obtainable from autopsy reports was dependent on the amount provided therein, but, overall, the standard and quality of the medico-legal reports was higher than the average for this type of autopsy.

Median age for children at death was 6 years, for adults it was 41 years.

Deaths in children were associated with congenital diseases (47%, 9/19), particularly of the heart and central nervous system. The autopsied children were not obese. Death in adults were associated with pregnancy (three cases in the study, but nationally 12/457 H1N1-associated deaths were noted), obesity (50% of adults had a body mass index ≥ 30 kg/m²), and chronic respiratory disease (12%, 6/49 adults). Diabetes did not emerge as a risk factor for death, but learning difficulties did.

Nearly all the deaths (94%, 64/68) were a consequence of H1N1 infection in the respiratory tract. In more than one-third (41%, 28/68) of the deaths, bacterial secondary infection was the significant complication; the pneumococcus was the most common agent identified (25%, 7/28).

Conclusions

Corroborated from the UK data, the major comorbidities associated with death from H1N1 infection were: obesity, chronic respiratory disease and pregnancy. Young age at death was confirmed. Congenital disease in children and learning difficulties in adults were also important, but diabetes was not.

This methodology of gathering data for research has potential for use in other public health questions, but is dependent on the co-operation of the medico-legal services (which have no accountability to the Department of Health or the NHS). The almost complete lack of academic

investigative consented autopsies is regrettable, and indicates a lack of interest among clinicians in the clinical autopsy process, and/or an unwillingness to approach relatives for such consent.

Recommendations for future research

1. Why are disabled children, pregnant women and obese adults particularly at risk of death?
2. Given the importance of secondary pneumococcal lung infection, what better preventive measures can be instituted?
3. How can patients *over*-diagnosed as H1N1 be better systematically identified, so that diagnostic protocols can be refined and thus reduce remediable fatalities?

Funding

The National Institute for Health Research Health Technology Assessment programme.

Chapter I

Introduction

This project was initiated in the summer of 2009, when the H1N1 epidemic had started in the UK, but the number of expected infections and of deaths was only conjectural.

The author was approached (a) because of a long-standing appointment with the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) and familiarity with perusing autopsy reports as part of clinical and death data audits; and (b) because of an interest in infectious disease and autopsy work, including investigation of adverse effects following immunisation (AEFI).

Research objectives

- To rapidly gather all the available clinical pathology information from autopsies performed on patients – adults and children – dying with known or suspected influenza A/H1N1 infection, across the UK.
- To evaluate comorbidities present in these deceased patients; correlate them with the H1N1-related pathology and treatment-associated pathology, determine their relative contributions, and estimate the significant features associated with death; and identify pre-mortem diagnostic confusions contributing to death.
- To evaluate the effects of treatment in these patients, including any adverse events following mass H1N1 vaccination.
- To post this information, anonymised, in real time, on a website available to health-care workers, followed by formal peer-reviewed publication.

In the event, the last two objectives were dropped. While the approval for the project was being sought (it came through at the end of November), it became evident that the numbers of deaths was not going to be as large as feared initially; thus real-time posting of information was not a priority. Secondly, during the epidemic and after, no evidence of any AEFI emerged, nor any side effects of the two anti-influenza chemotherapies used in the UK [oseltamivir (Tamiflu®, Roche) and zanamivir (Relenza®, GlaxoSmithKline)].

It should also be noted that, despite the anecdotal reports in newspapers of such cases, this study could not identify and analyse deaths where the presenting illness had been presumed to be H1N1 infection, but the actual clinical pathology turned out to be something different – and perhaps where the patient might have survived had H1N1 not distracted the carers. By definition, finding these cases systematically would have posed difficulties, and this was not in the original remit of the study.

Also the study did not include review of the histopathology samples taken at autopsy – which would have presented logistic issues – only review of the written autopsy report.

Time line for H1N1 morbidity and mortality in the UK [Health Protection Agency (HPA) data]:

- first case April 2009
- total reported infections > 30,000
- total deaths in UK = 457
- epidemic ends January 2010.

Chapter 2

Case collection

How many autopsies would there be?

The proportion of deaths with H1N1 infection that would have an autopsy was, of course, unknowable until the epidemic matured. It was assumed, from previous discussions on emergency planning since 2006 [Emergency Preparedness Clinical Liaison Advisory Group within the Department of Health, the author is the representative from the Royal College of Pathologists (RCPATH)] that, in the initial phase of attack, there would be many autopsies carried out while clinicians, virologists, pathologists and coroners familiarised themselves with the clinical pathology and other issues around evaluating persons suspected or known to have died from H1N1 infection. Thereafter, the autopsy rate would lessen as the perceived need declined – through more efficient case detection in life. It was also assumed that the core medico-legal need for coronial autopsy, i.e. identification and inclusion/exclusion of unnatural death (the main requirement of the medico-legal autopsy), would continue.

Secondly, it was not known what proportion of such autopsies would be medico-legal versus hospital/consented. This affected how the autopsy reports would be obtained, as those from consented autopsies would come under NHS standards for ethics and confidentiality, whereas those from medico-legal autopsies do not, being carried out independently of the NHS and Department of Health.

A guesstimate that 10% of H1N1 + deaths would be autopsied was made. It should be noted that in England and Wales, 22% of all deaths are subject to a coronial autopsy.¹ It was anticipated that because pandemic H1N1 would be a novel infection, categorised initially as Hazard Group 3 on the 1–4 scale of risk by the Advisory Committee on Dangerous Pathogens, pathologists and coroners might be reluctant to commission autopsies unless strictly necessary. Best practice guidelines on performing H1N1 + autopsies were promulgated in advance, on the websites of the RCPATH (www.rcpath.org) and the Association of Anatomical Pathology Technologists (www.aaptuk.org).

Collecting autopsy reports

Following consultation with the:

- National Institute of Health Research Health Technology Assessment programme
- RCPATH
- Coroner Society of England and Wales (CSEW)
- Crown Office and Procurator Fiscal Service (COPFS)
- Centre for Maternal and Child Enquiries (CMACE)
- HPA Swine Flu Unit
- National Research Ethics Service (NRES),

a sweep for autopsy reports relating to H1N1 deaths took place in the form of an e-mail to all active histopathologists in the UK (England, Wales, Northern Ireland, Scotland) to discover whether such autopsies were actually being performed, and how many were in children versus adults and were medico-legal versus consented. This produced a very positive response, encouraging the subsequent steps:

1. A later e-mail to all active histopathologists in the UK – with the letter seen in *Appendix 1* attached – to request copies of the autopsy reports by post, fax or e-mail.
2. The CSEW sent a similar e-mail (see *Appendix 2*) and a hard copy to all the coroner jurisdictions in England, Wales and Northern Ireland, with an official endorsement to collaborate by providing direct to the author the copies of the autopsy reports by post, fax or e-mail.
3. The CSEW also forwarded the e-mail to the COPFS, who also forwarded it to the forensic pathologists on their list, so that procurators fiscal in Scotland could collaborate.
4. Discussions with the CMACE which was, separately, undertaking a review of H1N1-related maternal deaths; this provided three autopsy reports, anonymised.
5. Discussion with the HPA Swine Flu Unit at Colindale also took place to identify possibilities of case-sharing of reported deaths of/with H1N1 infection, and possible information sharing about those who had

had an autopsy. These conversations proved fruitless as the HPA did not subsequently respond, and nothing more happened with the HPA for study data collection (however, see *Chapter 3, Secondary bacterial infection of the lung*).

Note: to encourage maximal participation and return of reports, the case definition for an autopsy report to be submitted was deliberately limited to one of:

- H1N1 infection was mentioned in any part (I or II) of the cause of death sequence by the pathologist
- H1N1 was proven to be present in pre- and/or post-mortem material.

In the event, all the submitted reports were on subjects proven, by standard virology polymerase chain reaction analysis, to have been infected with H1N1.

The study was not intended to, and did not, investigate those cases where H1N1 had been

clinically guesstimated in life, without virology confirmation, where the autopsy revealed different pathologies.

Confidentiality

Much time was spent during the study development period discussing how to manage patient confidentiality and anonymity. However, this aspect did not impede the inflow of autopsy reports. Only 2/68 (3%) of cases were hospital/consented autopsies (one adult, one child), for which it is an NRES requirement that the autopsy reports be submitted anonymised.

Nine of the 48 adult medico-legal case autopsy reports arrived anonymised (mostly from Scotland and Northern Ireland); all the others and all the child medico-legal case reports came with names and addresses indicated. The single consented child autopsy report was anonymised; that of the single adult consented case was not anonymous as the author performed the autopsy.

Chapter 3

Results

A total of 68 autopsy reports were received – 15% (68/457) of the total deaths that the HPA indicated had occurred due to H1N1 infection in the UK. These came from all over the UK (see *Table 2*), submitted by pathologists and coroners (often by both parties). The 68 reports represent all those H1N1 + autopsies that the author was aware had taken place through informal contact with pathologists, clinicians and coroners. There were 19 autopsies on children (age 0–15 years) and 49 on adults (age 16–68 years). However, the true total number of patients who died of H1N1-associated disease and were autopsied during the epidemic period is not knowable from this study survey.

The basic demographics and other data are summarised in *Table 1*. The origins of the patients, by NHS regions, are indicated in *Table 2*.

The overall median age of the cohort (two adult patients' reports had no age given) was 37 years. Given that the cases of H1N1-related death studied here were selected for having an autopsy, they may not be representative of the totality of those who died in the UK, but it is evident that they are considerably younger than the average age at death. In 2005, the NCEPOD study of coronial autopsies found a median age at death of 74 years.²

The causes of death in this cohort of patients

The causes of death were derived from the autopsy pathology. The data were from combined gross and histopathology examinations, plus the results of further bacterial and other investigations (all the cases had or had had H1N1 infection proven before and/or after death). These data

TABLE 1 Demographic and other data on the autopsy reports

	Children (0–15 years)	Adults (16+ years)
Number	19	49
Male:female ratio	7:12	29:20
Age – median (range)	6 years (7 months–15 years)	41 years (16–68 years) [Two adult patients: no age given]
Pregnant	0	3/20 females
BMI – median (range)	N/A	29 kg/m ² (14–68 kg/m ²) [Only 40/49 autopsies gave BMI data; one stated to be 'thin']
Medico-legal autopsy	18	48
Consented autopsy	1	1
Histopathology done	19 (100%)	42/49 (86%)
H1N1 diagnosed before/at autopsy	3/16	18/30 [One case not stated when]

BMI, body mass index; N/A, not applicable.

TABLE 2 Geographical location of the 68 autopsied patients, by NHS regions

Region	Children (0–15 years)	Adults (16+ years)
Scotland	0	2
Northern Ireland	1	2
Wales	0	1
North East	0	3
North West	1	6
Yorkshire	2	2
West Midlands	2	1
East Midlands	2	5
South Central	2	6
East of England	3	2
South East Coast	1	2
South West	1	5
London	4	9
Unknown (anonymised by CMACE)	0	3
Totals	19	49

were considered alongside the clinical and H1N1 virology data contained in the autopsy reports.

Because there is no universal standard for medico-legal autopsy practice, report formats, data and quality content, the results of this analysis are necessarily biased. Case definitions for primary H1N1 lung disease and secondary bacterial infection are partly subjective, but the best that can be obtained from the data. Reporting of comorbidities is also a minimum data set as, if the pathologist deemed a particular condition not relevant or interesting, or did not notice it at all, it would not be in the report.

Remarkably, the histology taking rate in this set of patients was high. For children, who are traditionally investigated fully, it was 100%. For the adult cases, 86% of the autopsies included histopathology (lung in all cases, plus other organs as deemed appropriate by the pathologist in consultation with the coroner). This contrasts with the 19% histology taking rate for non-homicide coronial autopsies found in the NCEPOD report into coronial autopsies, which sampled deaths in 2005.²

Evidently, the H1N1 epidemic in the UK was new, and pathologists and coroners believed it important to be more certain as to cause of death than, in other circumstances, they normally would be.

In addition, many cases (denominator unclear) had tissue samples tested in bacteriology and virology laboratories for co-infections – particularly bacterial lung infection. This enables presentation of the actual causes of death in four categories (Table 3):

1. H1N1-related influenza pneumonitis without secondary infection
2. probable H1N1 influenza pneumonitis, with later death under intensive care, where the autopsy necessarily will not be able to distinguish H1N1-only pathology from H1N1 plus another infection
3. secondary bacterial lung infection following from H1N1 infection that has damaged the airways and lung parenchyma
4. H1N1 infection around the time of death but incidental to the death.

TABLE 3 Categories of death in H1N1-infected persons

	Child N= 19 (%)	Adult N= 49 (%)
H1N1 pneumonitis only	10 (53)	23 (47)
H1N1 with long-term intensive care	0 (0)	3 (6)
Other lung infection following H1N1 infection	7 (37)	21 (43)
H1N1 incidental to death	2 (11)	2 (4)

Thus, H1N1 infection was responsible for the great majority (64/68 = 94%) of deaths in the cohort studied. About half of all the patients studied died of direct H1N1 infection of the airways and lung parenchyma; most of the rest had bacterial secondary infection in the lung.

In the autopsy reports, mention of specific anti-H1N1 chemotherapy was erratic. Thus there is no consideration here of possible toxic side effects, and no calculation of any clinical benefit provided by these therapies in persons with H1N1 infection.

Primary H1N1 influenza pneumonitis

The virus directly damages the lower airways and alveoli in a characteristic fashion, well-described in pandemic influenza. The two main lesions are necrotising bronchiolitis and acute lung injury (ALI; also termed diffuse alveolar damage). These can be identified only where there is histopathology of the lung, not from naked eye inspection.

From the 58 autopsy reports where these lesions were positively identified, or could be inferred from the microscopic descriptions, nine (16%) showed necrotising bronchiolitis, and 38 (66%) showed ALI. All the patients with necrotising bronchiolitis also had ALI, as has been noted in the Brazilian H1N1 autopsy study.³ The third lung pathology noted in Brazil, alveolar haemorrhage in association with ALI, could not be quantitatively assessed from the UK autopsy reports. The ALI prevalence in UK H1N1 cases is necessarily a minimum estimate for the reasons indicated above; a proportion was associated with secondary bacterial infection.

Secondary bacterial infection of the lung

The number of patients with pneumonia/bronchopneumonia in addition to H1N1 infection was 28/68 (41%). The specific infections identified result from culture of lung and/or blood in life or at autopsy; the aspergillus infections were identified histologically. The infections are indicated in *Table 4*.

TABLE 4 Pulmonary bacterial and fungal co-infections noted

<i>Streptococcus pneumoniae</i>	5
GAS	3
GAS + <i>Streptococcus pneumoniae</i>	1
<i>Streptococcus anginosus</i>	1
Total streptococcal cases	10
<i>Haemophilus influenzae</i>	2
<i>Staphylococcus aureus</i>	2
<i>Aspergillus</i>	1
<i>Aspergillus</i> + <i>Pseudomonas</i>	1
<i>Klebsiella</i>	1
<i>Pseudomonas</i>	2
<i>Serratia</i> + <i>Pseudomonas</i>	1
(These cases include long-term intensive care, i.e. hospital-acquired infection; the aspergillus infections were in patients with malignancy)	
Gram-positive cocci on histology, NOS	1
Presumed bacterial co-infection NOS, from gross/histology autopsy appearances, without specific culture	7
GAS, group A streptococcus; NOS, not otherwise specified.	

The total number of *Streptococcus pneumoniae* infections was six definite, plus one possible (gram-positive cocci on histology), giving a proportion of 7/68 total deaths (10%) or 25% of the deaths with secondary bacterial infection. Group A streptococcal infections numbered four, and there were two each with *Staphylococcus aureus* and *Haemophilus influenzae*. All of these specific infections were distributed across children and adults.

These prevalences are minimum estimates given the varied degrees of the investigations at autopsy and of the standards of autopsy reporting. But they

do indicate a very significant burden of secondary bacterial pathology on top of H1N1 infection of the airways and lung. Other studies have noted similar proportions of bacterial co-infections in their autopsy series: 38% in Brazil,³ 55% in New York, NY, USA,⁴ 26%–29% in the US Centers for Disease Control's study of referral autopsy case material.^{5,6} But each of these studies, including this UK study, has used different methodologies, so they are not strictly comparable.

The UK data do address and inform on a specific question that was raised by the Department of Health in preparation for future H1N1 epidemics: 'What proportion of deaths in H1N1-infected patients might be preventable by advance vaccination ("Pneumovax" against the pneumococcus) and by optimum antibiotic treatment during illness?'. The question was brought to the author by Dr Martin Utley (University College London conducting work on behalf of the Department of Health's Health Protection Analytical Team). This study indicates that the pneumococcus was the most common organism identified in children and adults.

Although positively identified in only six cases, the possibility has not been excluded that the pneumococcus was the agent responsible for all the other bacterial infections for which a different specific agent was not identified. Thus, potentially, the pneumococcus could be relevant in up to half (14/28) of all deaths where secondary infection of the lung occurred.

Other comorbidities in H1N1-associated death

Assessment of comorbidities was the prime aim of the UK autopsy study. Bacterial co-infection in the lung has been considered already. The other comorbidities identified in children (up to 15 years) were broadly different from those noted in adults.

Comorbidities in children

The clinical histories in the autopsy reports, along with the pathological findings, provided information on pre-mortem comorbidities and congenital conditions. Eleven of the 19 (58%) children had significant other diseases as shown in *Table 5*.

TABLE 5 Comorbidities reported in children: each line is one child

Failure to thrive; development failure; epilepsy
Pre-term birth at 27 weeks' gestation; congenital cytomegalovirus infection; hypothyroidism
Epilepsy; cerebral palsy; encephalopathy
Cerebral palsy
Complex congenital heart disease – surgically corrected
Microcephaly; epilepsy; congenital heart disease; chromosomal deletion syndrome
Microvillous inclusion disease
Still's disease; on steroid therapy; macrophage activation syndrome
Hypertrophic obstructive cardiomyopathy
Marfan's syndrome
Cerebral palsy, due to kernicterus; hydronephrosis; renal dysplasia
Glue ear

Congenital central nervous system (CNS) disease, epilepsy and congenital cardiac disease were the outstanding comorbidities associated with death from/with H1N1 infection. If we include the four adult patients with persisting congenital heart and CNS problems (see *Table 6*) and who died at ages 16–49 years, then the burden of congenital disease as a comorbidity affecting outcome in H1N1 infection is even more significant.

Only one child had an immunosuppressing condition (long-term steroid therapy).

These proportions are necessarily minimum data, from the nature of what is put into or excluded from an autopsy report. But the autopsy reports on the dead children appeared to be universally comprehensive (in contrast to those on adults), and thus these data are probably representative.

Comorbidities in adults

The clinical histories in the autopsy reports, along with the pathological findings, provided information on pre-mortem comorbidities and congenital conditions. Such data are incomplete as it is not a requisite to insert any clinical history information, nor a clinicopathological summary, into medico-legal autopsy reports.

In *Table 6* which lists noted comorbidities, the following conditions were omitted: history of smoking ($n = 2$ only, evidently a minimum number), asthma, obesity and pregnancy.

The last three were considered later ('specific comorbidities') as they became globally apparent in clinical reports as the pandemic unfolded.

A total of 39/49 adults were noted to have comorbidities. Several patients had more than one, so the totals are > 39 cases.

The range of conditions noted was broadly comparable to those seen in other nations' studies and small case series. Apart from the very few cases where the pathologist considered the H1N1 infection to be coincidental to the cause of death, all of these comorbidities were of secondary importance compared with H1N1 infection.

The most common conditions were hypertension, other cardiac disease and alcohol abuse. No patients with chronic renal failure were identified in the study, nor any with a solid-organ transplant.

TABLE 6 Comorbidities in adults

Hypertension = 10
Ischaemic heart disease = 3 (one had previous coronary artery bypass graft)
Infective endocarditis = 1
Diabetes = 4
Hypercholesterolaemia = 1
Stroke = 1
Pulmonary fibrosis = 2 (idiopathic = 1; industrial = 1)
Congenital heart disease = 1 (ventriculo-septal defect with pulmonary hypertension)
Congenital CNS disease = 3 (global retardation, epilepsy and hypothyroidism = 1; cognitive decline and encephalomalacia, with spherocytosis = 1; cerebral palsy, epilepsy, ventriculo-peritoneal shunt = 1)
Scoliosis = 2
Malignancy at autopsy = 3 [myeloma = 1; B-cell lymphoma = 2; (previous treated acute myeloid leukaemia = 1)]
Rheumatoid arthritis = 2
Liver cirrhosis = 3
Recent surgical treatment = tonsillectomy and uvuloplasty = 1
Alcohol abuse = 4
Illicit drug abuse = 3 (IVDU, methadone = 2; unstated = 1)
Schizophrenia or psychosis = 3
Depression = 3
Mental health problems, NOS = 1
IVDU, intravenous drug user; NOS, not otherwise specified.

Specific comorbidities

Early on during the pandemic, it became evident from case reports and small series that a number of specific medical conditions appeared to be over-represented in persons who were seriously ill with H1N1 infection. These conditions include: obesity, diabetes, pregnancy, asthma, human immunodeficiency virus (HIV) co-infection and immunosuppression from cancer therapy. Sickle cell disease was also considered in some centres.

In this UK study, there were no recorded HIV-infected or sickle-associated fatalities. Cancer comorbidity is listed in *Table 6*, but does not appear more frequent than one might expect from a cohort of deaths in this age group. Liver cirrhosis is another immunosuppressing condition, and was noted in three patients (one of them stated to be alcoholic).

Diabetes was highlighted early on as a potentially significant comorbidity. *Table 6* indicates only four patients (necessarily a minimum estimate), but there is no suggestion from the autopsy reports that the proportion of diabetics exceeded the national prevalence. More importantly, the clinical study from Birmingham, UK⁷ found no excess of diabetic patients among those admitted to hospital and intensive care, compared with the local (high) prevalence of that condition.

Table 7 indicates specific comorbidities identified in adult patients.

TABLE 7 Specific comorbidities in adults

	Adults N = 49
Obesity (BMI ≥ 30 kg/m ²)	20 = 50% where BMI or habitus known 11 females, 9 males
Recorded history of asthma or chronic obstructive pulmonary disease	6 = 12% Three females, three males
Recorded clinical history of 'learning difficulties'	8 = 16% 5/20 females (25%), 3/29 males (10%)
Pregnancy	3/20 (15%) females Two died post partum at 29 and 33 weeks' gestation One died at 20 weeks, fetus undelivered
BMI, body mass index.	

Obesity

Obesity was a noted comorbidity only among adults, not children. The median body mass index (BMI) in adults was 29 kg/m² (range 14–68 kg/m²; see *Table 1*), but only 40/49 autopsies gave BMI data; one additional patient was stated to be 'thin'. Nonetheless the proportion of patients with a BMI of ≥ 30 kg/m² was high at nearly 50%; eight patients (20% of all assessable adults) were morbidly obese with BMI > 40 kg/m².

This association of obesity with death from H1N1 infection has been noted globally. The mechanisms are uncertain, but those proposed include:

- mechanical variables relating to breathing
- sleep apnoea syndrome
- pulmonary hypertension
- immunosuppression caused by obesity itself.

Asthma

Asthma and chronic obstructive pulmonary disease are biologically reasonable comorbidities that could increase morbidity and mortality in H1N1 lung infection. However, the data in this study do not show a high prevalence among the 49 adults (6 = 12%). The real prevalence may be higher, but (a) the condition may not be mentioned in the autopsy report clinical history, and (b) if asthma-related histopathology were present, the pathologist may not mention it when other pathologies (ALI and secondary infections) are present.

Two other adults were noted to have chronic fibrosing lung disease, and two had scoliosis, which similarly could impair the host response to H1N1 infection.

Pregnancy

During the H1N1 pandemic, pregnant women were quickly realised to be a vulnerable group, with high admission rates to intensive care for ventilatory support⁸ and high mortality.

This study identified three autopsied women who died after delivery (2) or while still pregnant (1). There is a concurrent study of H1N1 and maternal mortality in the UK, undertaken by the CMACE. This has not yet been published.

Twelve maternal deaths related to H1N1 infection were reported to the CAMCE during the 2009–10 epidemic, and the three cases in this study appear

to be the only ones who had an autopsy. Two of the women died in intensive care from H1N1 influenza pneumonitis after delivery; they had comorbidities of scoliosis and recreational drug abuse with stroke, respectively. The third woman died still pregnant, of secondary bacterial infection on top of H1N1 infection.

Proportionately, pregnancy stands out as the pre-eminent risk factor for death with H1N1 infection. Of all the UK H1N1-associated deaths, 2.6% (12/457) were pregnant women; yet maternal deaths overall account for only 0.02% of all deaths in the UK (CMACE data).^{1,9} This, crudely, suggests a $\times 100$ relative risk of death among pregnant women.

Learning difficulties and mental health problems

These have not been noted in other series. The high prevalence of congenital CNS conditions among the dead children, plus the clinical information in the adult autopsy reports concerning 'learning difficulties' and psychiatric conditions (see *Table 6*) suggest that this group of patients is vulnerable to severe H1N1 infection. The mechanisms might include (a) an associated impairment of immune defences to infection, and (b) problems in accessing health care.

Specific other pathologies

A few other specific conditions are worth mentioning as arising from the data accrued during this autopsy report of H1N1-associated deaths.

Venous thromboembolism

Many of the patients were hospitalised as opposed to dying in the community. But only two adult patients were noted to have pulmonary thromboembolism from deep vein thrombosis; both died with primary H1N1 pneumonitis. One was obese (small emboli found in the lungs), the patient with massive thromboembolism had a BMI of 26 kg/m².

Thus venous thromboembolism does not appear to be over-represented among these deaths, despite the high prevalence of obesity.

Haemophagocytosis

The macrophage activation syndrome, or haemophagocytic syndrome, is a documented complication of pandemic influenza and H5N1 influenza human infection, and was reported in other studies during the 2009–10 H1N1 pandemic.

Only 13/61 autopsy reports with histopathology mentioned bone marrow evaluation, and haemophagocytosis was stated to be present in 4/13.

Myocarditis

There is debate over whether H1N1 and other type A influenza viruses directly cause myocarditis. In this study, 3/19 children were stated to have myocarditis on histopathology, in association with H1N1-related influenza pneumonitis. But despite virology in two cases, H1N1 was not isolated from the heart tissue. Unfortunately, in investigating presumed acute viral myocarditis, in all age groups, it is uncommon to identify the specific agent in the tissue. No adults were noted to have myocarditis.

Chapter 4

Commentary (discussion)

The presentation of results from this study has included discussion on the specific clinicopathological entities that were found, pathogenesis, and the comparative epidemiology of H1N1-related disease as derived from the published pathological literature.^{3–6}

The small sample number (68 reports from 457 deaths) limits further speculation, but there is no a priori reason to consider the data unrepresentative of what happened in the UK. However, there are two overarching issues that emerged from the process of this study, which relate to gathering information on deaths, and how autopsy practice in the UK has changed in recent decades.

The author found it unexpectedly easy to access these H1N1-related autopsy reports. Fellow pathologists, coroners and procurators fiscal went out of their way to help and appeared glad to be contributing to a national epidemiological study. As many of them pointed out, this might be one of the few occasions when medico-legal autopsy reports are actually beneficial to public health. Modern communications and information technology systems undoubtedly assisted here. E-mail is common to all, and a large number of the autopsy reports were attached to e-mail, thus enabling rapid transmission with minimum office hassle.

A second helpful factor was the absence of the need to anonymise the medico-legal autopsy reports, again resulting in minimum trouble in the transmission of reports to the author's office. Had there been more hospital/consented autopsies (see below), the author suspects that the necessary anonymisation at source plus the requirements of the NRES might have significantly impeded the

enthusiasm of pathologists to assist with providing the case data.

The 2009–10 H1N1 epidemic in the UK might have been 'special' and possibly unique for various reasons, but the collective positive response from those involved in death and autopsy investigations does suggest that this type of targeted approach could be used in the investigation of other scenarios of death of concern to UK public health – so long as the questions are kept simple.

Finally, the fact that there were so few consented autopsies in adults or children is very worrying for the future of autopsy pathology and clinical research in the UK. It follows the trend since the 1970s for clinicians not to request autopsies, and the tacit assumption that medico-legal system autopsies can fill the gap. All the comparative studies of pre- and post-mortem diagnoses since the beginning of the twentieth century come to the same conclusions, that in up to one-quarter of deaths, the pre-mortem (clinical) diagnosis is seriously incorrect compared with a full autopsy examination diagnosis.¹⁰ So the apparent unwillingness of clinicians to ask relatives for autopsies after deaths from this 'new epidemic disease' of H1N1 infection does not inspire confidence in the processes of clinical investigation and audit. Medico-legal autopsies have a very narrow remit, namely and primarily to identify potential unnatural causes of death, and to indicate whether or not there is a need for a public inquest.¹¹ They are not intended or funded to undertake detailed clinicopathological investigations of medical deaths in general. The fact that, from these results, they mostly did so is commendable – but it was not and should not be expected from the system.

Chapter 5

Conclusions and summary

This review of autopsied H1N1-infected persons who died in the UK during the 2009–10 epidemic has highlighted several clinicopathological and autopsy-related issues, despite it being an incomplete medical study of what happened during the epidemic. We have no true measure of whether the cases selected for autopsy are representative of the total deaths in terms of pathology and comorbidities.

1. A higher than expected number of deaths among H1N1-infected persons were subjected to autopsy (15%).
2. Overall, these autopsies, nearly all medico-legal in origin, were performed and reported to a higher standard than pertains for 'routine' medico-legal autopsy work. In particular, a very high tissue sample rate occurred, which enabled this study's description of the underlying lung pathology.
3. Despite informal encouragement from all levels within the health service, very few hospital/consented autopsies were performed on the patients who died with H1N1 infection. This is disappointing, and an indictment of the current status of autopsy within the medical firmament. The reasons for this low rate are beyond the remit of this report.
4. The median age at death of those autopsied was young, 37 years, with a median of 41 years for adults (16–68 years).
5. Nearly all the deaths were a consequence of H1N1 infection in the respiratory tract.
6. In more than one-third of the deaths, bacterial secondary infection was the significant complication, of which the pneumococcus was the most common agent identified. This may have implications for the specific management of future epidemics of influenza.
7. Comorbidities were common among both child and adult patients.
8. In children, and to a lesser extent in adults, the major comorbidities were congenital disease affecting the CNS and the heart.
9. In adults, the most important comorbidity was pregnancy in women: this important datum comes not directly from the autopsy report study, but from combining it with the CMACE data.
10. In adults, obesity in both sexes was the second major comorbidity. Chronic respiratory disease, particularly asthma, was also important. Diabetes was not a significant comorbidity.
11. In adults, patients with 'learning difficulties' appeared to be over-represented, speculatively related to problems in accessing health care.

Future research questions

These results reinforce the need to enquire further into the pathogenesis of severe and fatal H1N1 disease, and the circumstances of clinical presentation and rapid evaluation in a time of epidemic influenza.

- Why are disabled children, pregnant women and obese adults particularly at risk of death?
- How effective are the specific antiviral drugs given to patients?
- When should they be optimally given to presenting patients?
- Given the importance of secondary pneumococcal lung infection, what better preventive measures can be instituted?
- How better can patients *over*-diagnosed as H1N1 be systematically identified, so that diagnostic protocols can be refined and thus fatalities remediable be reduced?



Acknowledgements

Sebastian Lucas sought and collected all the data with direct help from the National Institute of Health Research, RCPATH, CSEW, COPFS and

CMACE. He collated and analysed all the data and drafted the report.



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Appendix I

Swine flu (H1N1) autopsies in the UK – a national autopsy-based study of comorbidities: letter I

[full title: NIHR project 09/84/18 – Predictive clinicopathological features derived from systematic autopsy examination of patients who die with A/H1N1 (pandemic flu) infection]

Letter #1 – to pathologists

You were one of the many pathologists who kindly and promptly informed me that they had performed a swine flu positive autopsy. The RCPATH IT department excelled itself in sending out the initial flash email.

The good news is that I have obtained, from the NHS National Institute for Health Research (NIHR), the go-ahead to pursue the study. Specifically I have been granted:

- National Research Ethics Service approval (ref 09/H0803/150)
- Local (Guy's & St Thomas') ethical approval
- 2PAs funding for six months to complete the project
- Encouragement and approval from the senior officers of the Coroners Society of England & Wales
- Approval from the Health Protection Agency (HPA) to collaborate on the reporting of swine flu deaths, and dissemination of information from this study.

If you wish to see the evidence of these, I can email you the documents.

So, I would be grateful if you could send me – by post or fax or email attachment – the autopsy reports of all the swine flu cases that you have performed. The inclusion criteria for cases are:

- those with H1N1 infection, proven before or after death, and those where swine flu is unproven but most likely to have been present
- those where H1N1 is a minor pathology, as well as those in which it is the immediate cause of death
- cases where the patient had lingered long-term in ICU before dying
- all ages from infancy to old age
- consented and coronial/fiscal autopsies.

It would be very useful to have the clinical history, as documented by you in the autopsy report. If you do not include such histories in your reports, I would be grateful to see the written information presented to you by coroners – if that is feasible.

Confidentiality is critical, and is in most cases is my problem. Most of the autopsies are coronial, which have no NHS-related confidentiality issues. For the coronial cases, I will anonymise the cases when entering the data in the database, so please send the original un-edited autopsy reports.

For the consented autopsy cases, can you let me know if you have one; then my colleague in the local research & development unit can take up the case with your Trust R&D unit to confirm their agreement to send me the case information. What I will then ask you to do is anonymise the autopsy report but retaining the essential demographic information: *viz* month & year of death; sex; gender; ethnicity; age to the nearest year (or nearest month if under 1 yr old).

If you perceive any problems with acceding to this request for autopsy reports – e.g. from your coroners – please let me know, and we can find a way round the problem.

All the information gained and promulgated from the study will, of course, be anonymous.

Yours sincerely, and thank you in advance

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Appendix 2

Swine flu (H1N1) autopsies in the UK – a national autopsy-based study of comorbidities: letter 2

[full title: NIHR project 09/84/18 – Predictive clinicopathological features derived from systematic autopsy examination of patients who die with A/H1N1 (pandemic flu) infection]

Letter #2 – to coroners and procurator fiscals

Rationale

At the request of the National Institute for Health Research (the Health Technology Assessment section), I am conducting a review of the autopsy reports on UK patients who have died of or with **swine flu (H1N1 infection)** since April 2009. This is to formally describe what happened in 2009–2010, with particular reference to co-morbidities in the patients who died.

It will enable the most complete description of clinical pathology of the recent swine flu epidemic, and should therefore have practical lessons for any similar future outbreaks, and particularly how we investigate the deaths. The associations with asthma, obesity and pregnancy are important, but we need to know about other possible co-morbidities that may be revealed only by autopsy.

Authorization

I have obtained, from the NHS National Institute for Health Research (NIHR), the go-ahead to pursue the study. Specifically I have been granted:

- National Research Ethics Service approval (ref 09/H0803/150)
- Local (Guy's & St Thomas') ethical approval
- 2PAs (sessions a week) funding for six months to complete the project
- Encouragement and approval from the senior officers of the Coroners Society of England & Wales, and from the Crown Office and Procurator Fiscal Service in Scotland
- Approval from the Health Protection Agency (HPA) to collaborate on the reporting of swine flu deaths, and dissemination of information from this study
- Support from the Royal College of Pathologists to undertake the study; their IT department sent a flash email to all pathologists, which prompted >350 replies, including notice that at least 50 H1N1+ autopsies had been done by Christmas 2009.

So, I would be very grateful if you could send me – by post or fax or email attachment – the autopsy reports of all the swine flu cases – as defined below – that have been examined under your jurisdiction.

The inclusion criteria for cases are:

- mention of 'swine flu' or 'swine influenza' or 'H1N1 infection' in any part of the cause of death, i.e. in Part 1 or in Part 2
- any age from infancy to old age.

It would be very useful to have the clinical history, as documented in the autopsy report – if that is feasible.

Confidentiality is critical, and is my problem. For these Coronial/Fiscal cases, I will anonymise the cases when entering the data in the database, so please send the original un-edited autopsy reports. This procedure is in accordance with NHS instructions.

All the information gained and promulgated from the study will, of course, be anonymous.

Yours sincerely, and thank you in advance

Professor Sebastian Lucas

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