An Epidemiological Survey of Langerhans Cell Histiocytosis in Children in the United Kingdom and Republic of Ireland

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Abstract

Langerhans Cell Histiocytosis (LCH) is a rare disease of the immune system which, in children, is treated mainly by oncologists. It has several forms ranging from spontaneously regressing localised bony disease to life-threatening multi-organ failure. Mortality is low but children may be left with long-term sequelae. LCH is inconsistently registered by cancer registries and although the Children's Cancer and Leukaemia Group (CCLG) records cases, its incidence in the UK and Republic of Ireland was previously unknown, prompting this national survey to describe the epidemiology of LCH in children.

Three sources of case ascertainment were used: the British Paediatric Surveillance Unit, a Newcastle-based postal survey of other clinicians, and the CCLG. National deaths data were also obtained. Questionnaires were sent to reporting clinicians to obtain further information and to follow up cases one and two years after diagnosis. The completeness of ascertainment was estimated by capture-recapture methods; the spectrum of disease was described; possible associations, event-free survival and mortality were assessed.

Each source uniquely ascertained cases and completeness was estimated at 93%. 94 children were identified giving an incidence rate, comparable with other European reports, of 4.1 per million per year (aged 0-14 years). 67% of cases had SS bone disease and 26% had multi-system disease. More cases than expected were diagnosed in spring ($p=0.04$) and there was a higher than expected proportion of mixed/other ethnicity children than in the general population ($p=0.027$). At the end of the study, 91% had no active disease and 18% had sequelae. Mortality was 3.2%.

This is the first national study to use a well-established prospective method of case identification. The importance of multiple sources of ascertainment was demonstrated. Although the data and number of cases were limited, the results above, and other observations, indicate the need for further follow up and larger studies.

Dedication

This thesis is dedicated to my parents, Bill and Jane Burnell-Higgs.

Acknowledgements

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Finally, I would like to thank my family and friends for their interest and for keeping me going - especially my husband, Paul, for his love and support (and cooking!) particularly in the last year, and my daughter, Julia, for her fine example of perseverance and hard work.

Table of Contents

List of Tables

List of Figures

Abbreviations

A&E	Accident and Emergency
ACTH	Adrenocorticotropic hormone deficiency
ADP	Adenosinetriphosphatase
AIC	Aikaike Information Criterion
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
ART	Artificial reproductive technology
ASR	Age-standardised rate
BIC	Bayesian Information Criterion
BPSU	British Paediatric Surveillance Unit
CCLG	Children's Cancer and Leukaemia Group
CI	Confidence interval
CMO	Chief Medical Officer
CNS	Central nervous system
CPSP	Canadian Paediatric Surveillance Program
C-RA	Capture-recapture analysis
CR	Centres of reference
CSO	Central Statistics Office (Ireland)
DCW	Digital Chart of the World
DI	Diabetes insipidus
DIN	Doctors' Independent Network
ESP	European standard population
ESRI	Environmental Systems Research Institute
FSH	Follicle stimulating hormone
GHD	Growth hormone deficiency
GIS	Geographic information system
GOR	Government office region
GOSH	Great Ormond Street Hospital
GPRD	General Practice Research Databases
H&E	Hematoxylin and eosin
HES	Hospital episode statistics
HLA	Human leukocyte antigen

HLH	Haemophagocytic lymphohistiocytosis
HPS	Health Protection Scotland
HRT	Histiocytosis Research Trust
HUMARA	Human androgen receptor gene assay
ICCC	International Classification of Childhood Cancers
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases for Oncology
IR	Incidence rate
IRAS	Integrated Research Application System
LCH	Langerhans cell histiocytosis
MAUP	Modifiable areal unit problem
MESH	Medical subject heading
MF	Multifocal disease
MLE	Maximum likelihood estimator
MREC	Multi-research ethics committee
MS	Multi-system disease
NCL	Newcastle
NHS-CR	National Health Service Central Register
NIGB	National Information Governance Board
NORD	National Organisation for Rare Diseases
NRCT	National Register of Childhood Tumours
NRYPMDR	Northern Region Young Persons' Malignant Disease Registry
NUE	Nearly unbiased estimator
ONS	Office for National Statistics
PAHO	Pan-American Health Organisation
PIAG	Patient Information Advisory Group (now NIGB)
RCPCH	Royal College of Paediatrics and Child Health
RoI	Republic of Ireland
RO-	Multi-system disease without risk organ involvement
RO+	Multi-system disease with risk organ involvement
SE	Standard error
SEER	Surveillance Epidemiology and End Results
SS	Single system disease
TSH	Thyroid stimulating hormone

TYA	Teenage and Young Adult
UF	Unifocal disease
UKCCSG	UK Children's Cancer Study Group (now CCLG)
WHO	World Health Organisation

Chapter 1. Introduction

1.1 Why study Langerhans cell histiocytosis?

Langerhans cell histiocytosis (LCH) is a rare disorder of the immune system that has multiple patterns of presentation ranging from spontaneously regressing lesions to a multi-system form with organ failure. The cause of the disease is unknown. Although there have been a few international and regional studies of geographically defined populations, most publications on LCH have been of case reports or studies of hospital series and the epidemiology of LCH is under-researched [1-3]. Clinical studies of LCH in children had been carried out for many years in the UK and Republic of Ireland but the incidence of the disease was not known. As well as describing occurrence, an observational epidemiological study is the first step in countering the lack of information about a disease, and it may explain the pattern of the disease by identifying possible aetiological factors. The rarity of disorders such as LCH makes them difficult to study and identification of cases from a large population is required to give a sufficient number of cases to obtain meaningful data. A national study was therefore initiated and an epidemiological survey of LCH in children in the UK and Republic of Ireland began in 2003. The aims of the study, which are described further in section 1.8, were to establish the incidence of LCH over two years, describe the spectrum of disease and assess the outcome.

The approach taken to carry out the study was informed by the nature of the disease itself – its various forms, the clinicians who treat it, how it is classified, diagnosed and registered and the possible methods of ascertaining cases in the UK. These are described in the remainder of this chapter. The rationale and objectives of the study are stated and an outline of this thesis is presented. A more detailed description of the disease, including its symptoms and characteristics and treatment and outcome, are given in Chapter 2 with a review of epidemiological studies.

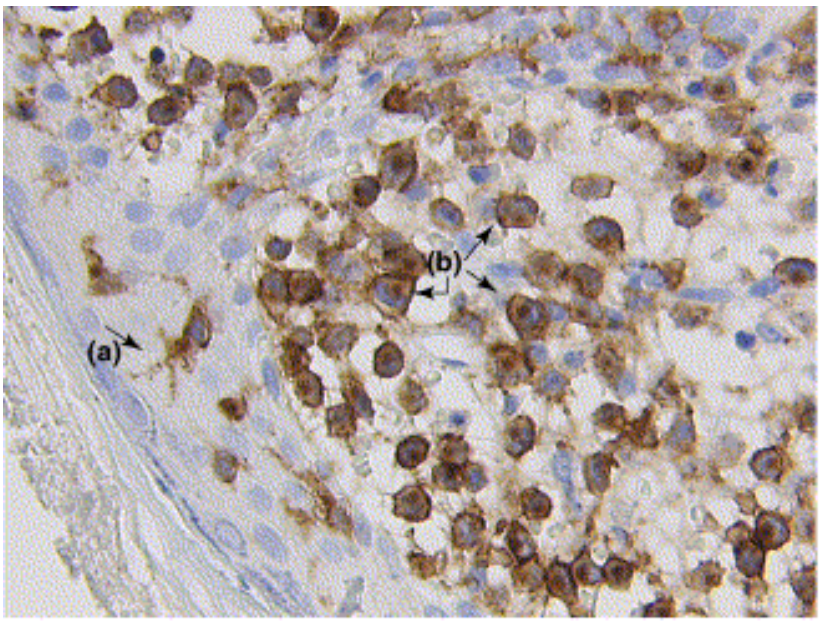
1.2 Langerhans cells and LCH

Langerhans cells were first described by Paul Langerhans in 1868 as neuronal cells but it was not until the 1970s that they were demonstrated to form part of the immune

system [4]. They are dendritic cells, originating in the bone marrow, and are normally found in the skin, lymph nodes and main airways [5, 6]. They present various antigens and are involved in stimulating the immune response. LCH cells appear to be an immature form of Langerhans cells with a more rounded shape (figure 1.1) [7]. LCH is commonly found in skin, bone and the pituitary gland, and may also affect the lungs, intestines, liver, spleen, bone marrow, lymph and brain – in tissues where Langerhans cells are not normally found. The features of disease are accumulation and proliferation of LCH and other immune cells and overproduction of cytokines, causing tissue damage and inflammation resulting in fibrosis and scarring [7, 8]. Identification of the LCH cell is important in diagnosing the disease (see section 1.4 below). It is not known how the various organs described above can be affected by LCH when Langerhans cells are normally restricted to the epithelium. However, there has been a recent suggestion, based on animal studies, that LCH cells and Langerhans cells may develop from different subsets of mesenchymal cells, the subset giving rise to LCH being present in most tissues affected by the disease [9].

Although LCH is a disorder of the immune system, it is treated mainly by paediatric oncologists and haematologists. However, since a variety of organs may be affected, a child may present with a wide range of symptoms and referral may be either to a general paediatrician or one or more of a number of specialists. There is world-wide collaboration in the treatment of LCH because of its rarity, heterogeneous forms and response to treatment, and international protocols have been established for many years. Treatments range from observation through localised surgery to chemotherapy and immunotherapy.

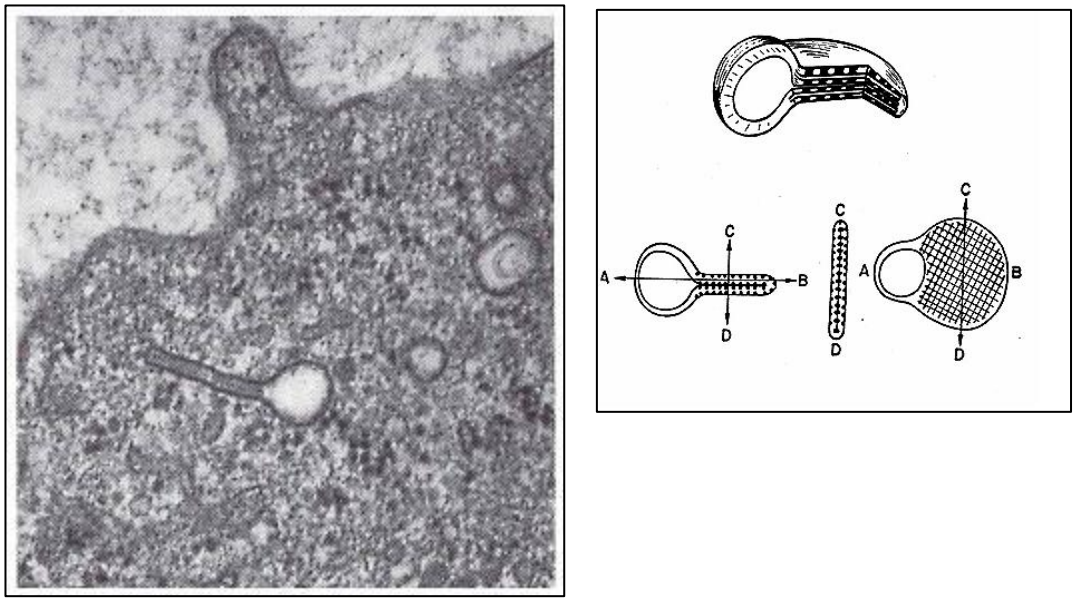
Figure 1.1 Langerhans cell and LCH cells (from Laman et al [7])



LCH skin stained for CD1a, showing (a) normal Langerhans cells with dendritic morphology in epithelium, and (b) an accumulation of rounded LCH cells.

Figure 1.2 Birbeck granules within Langerhans cells [10]

(a) (b)



Electron microscopy (a) and schematic (b) showing Birbeck granules with characteristic tennis-racket shape which may appear rod-shaped in certain planes.

1.3 Types and classification of LCH

The disease has several different forms ranging from spontaneously healing bone lesions to a progressive multi-system disorder which may be fatal [2, 11]. In the late 19th and early 20th century clinicians in the US and Europe noted similarities in cases leading to the recognition and naming of the condition and its different forms as shown below.

- eosinophilic granuloma (bone)
- Hand-Schuller-Christian disease (multifocal bone, diabetes insipidus, proptosis)
- Letterer-Siwe disease (disseminated)

The history of LCH has been described in detail by Coppes-Zantinga and Egeler [12]. In the 1950s the term Histiocytosis X was introduced to include the different forms of LCH based on common pathology – all types having Birbeck granules which are found in Langerhans cells (figure 1.2). The disease is also known as infantile acute reticuloendotheliosis, Hashimoto–Pritzker disease (a self-healing skin variant) and Langerhans cell granulomatosis. The various forms are not exclusive and may overlap with progression between types. However, since all variants of LCH have Langerhans-like cells in common, the Histiocyte Society proposed the term Langerhans cell histiocytosis and it has been in use since 1985 [13]. LCH is the most common of a group of histiocytic disorders. They were classified by the Histiocyte Society and revised by Favara et al in 1997 [14, 15]. The classification is given in table 1.1 showing their relationship to malignancies.

Table 1.1 Classification of histiocytic disorders (adapted from Favara et al [14, 15])

Langerhans Cell Histiocytosis

non-Langerhans Cell Histiocytoses

- Juvenile Xanthogranuloma Family
  - Cutaneous – Juvenile xanthogranuloma
  - Cutaneous and systemic – Xanthoma disseminatum
  - Systemic – Erdheim-Chester disease
- non-Juvenile Xanthogranuloma Family
  - Cutaneous – Solitary reticulohistiocytoma
  - Cutaneous and systemic – Multicentric reticulohistiocytosis
  - Systemic – Rosai-Dorfman disease

Haemophagocytic Lymphohistiocytosis

- Familial (congenital)
- Secondary (reactive)

Histiocyte Lineage-related Malignancies

- Leukaemias
  - Acute myelomonocytic and monocytic
  - Chronic myelomonocytic/juvenile myelomonocytic leukaemia
- Monocytic and histiocytic sarcomas

To put LCH in a wider context, the classification used by the World Health Organisation (WHO) in the latest version of their International Classification of Diseases (ICD) series (Version 10 (ICD-10)) is shown in Appendix A [16]. The classification takes into account the severity of the different forms of the disease. Letterer-Siwe disease, a disseminated form of LCH, is found among the group of "Malignant neoplasms of lymphoid, haematopoietic and related tissue" while the other forms are found among "Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism".

The current version of the International Classification of Diseases for Oncology (ICD-O-3), a specialty-based adaptation of the ICD series which is used mainly in cancer registries, includes one form of LCH (disseminated) as a malignant neoplasm. ICD-O-3 is based on ICD-10 but provides greater detail for neoplasms since it includes an additional code for the histological type [17]. The site (topography) and the histology (morphology) are coded from information usually obtained from a pathology report. The fifth digit (after /) in the morphology code is a behaviour code which indicates whether a tumour is malignant, benign, in situ, or uncertain whether benign or malignant. Those with /1 are usually considered of uncertain borderline behaviour. The ICD-O-3 morphology codes for LCH are as follows.

9751/1 Langerhans cell histiocytosis NOS
9752/1 Langerhans cell histiocytosis Unifocal
9753/1 Langerhans cell histiocytosis Multifocal
9754/3 Langerhans cell histiocytosis Disseminated

This coding system is particularly useful for children's cancers which have more heterogeneous histological sites and types than adult cancers which are generally classified by the primary site of the tumour [18]. However, if registration of LCH cases by cancer registries is based on whether the disease is coded as a malignancy, then only cases of disseminated LCH (Letterer-Siwe disease) are likely to have been included.

Children's cancers have been grouped, using these oncology codes, into twelve categories of childhood cancers – the International Classification of Childhood Cancers (ICCC). This was designed to be used in international, population-based, epidemiological studies and cancer registries where the use of an international grouping

system is important in ensuring data comparability. Since the inclusion of LCH is controversial, it is not in the ICCC classification and data on an international scale are not available [19]. Some registries such as the German Cancer Registry have, however, adopted the Birch and Marsden classification, on which ICCC was originally based, and which includes LCH in the group of reticuloendothelial neoplasms [2, 20]. The version used by the UK Children's Cancer and Leukaemia Group (CCLG) also includes an extra group (XIII) for non-malignancies including all LCH variants and haemophagocytic lymphohistiocytosis (HLH) [21].

1.4 Diagnosis

Eligibility of cases in a disease registry or epidemiological study depends on well-defined diagnostic criteria. The variety of forms of LCH and its rarity may increase the possibility of it being mistaken for other diseases such as osteomyelitis, seborrheic dermatitis or juvenile xanthogranuloma. Histological diagnosis of LCH is therefore important for confirmation of disease although clinical judgement may be used in some cases.

LCH can be diagnosed definitively by characteristic histology, positive staining for antigen CD1a and the presence of Birbeck granules (figure 1.2) [13, 14]. Since positive staining can occur in normal Langerhans cells it is important to examine lesional cells only. Two or more other positive stains (S-100 protein, adenosinetriphosphatase (ADP), D-mannoxidase or peanut lectin, in addition to conventional histology (staining with Hematoxylin and Eosin (H&E)), and clinical findings may be sufficient for a presumptive diagnosis of LCH [22]. Although desirable, a biopsy may be unfeasible because of the location of the lesion or because clinical features suggest possible resolution. In the case of LCH of the pituitary gland and some bone lesions, diagnosis may be made by characteristic appearances on X-rays or CT scans (with additional tests for pituitary dysfunction).

Diagnosis may be made accidentally in some cases, particularly of isolated disease. For example, Leavey et al reported that 6/22 unisystem cases in a hospital series in Dublin were diagnosed from X-rays for an unrelated condition [23].

1.5 Sources of LCH cases

Disease-based registers, of which there are reported to be over 250 in England, collect data on all cases of a particular condition for a defined geographic population [24]. Registries rely on the cooperation of clinicians to report cases although eligible cases may be actively sought. Case registration is based on defined classification and diagnostic criteria. Additional sources may be used to ascertain cases, such as death certificates, or data may be cross-checked with other registries or study groups [2, 25]. Registries and other potential sources of LCH cases are discussed below.

1.5.1 National and regional studies

In both national and regional incidence studies of LCH most authors obtained data from malignancy registers [1-3]. Three reports from France, Hungary and Germany (described in section 2.3.1) used data from national registries which have consistently recorded cases of LCH [3, 26, 27]. In other studies, sources of data were paediatric oncology or haematology centres with additional cases identified from paediatric or other specialties [1, 28]. Approaching other specialists optimised the identification of cases, for example, of bone LCH which may only have been seen by orthopaedic surgeons. Estimations of the completeness of ascertainment of LCH and cancer cases using several sources were reported to be 95% and 90% in the children's cancer registries in Germany and Switzerland respectively and 97% for LCH cases in France [3, 20, 29].

1.5.2 UK and Republic of Ireland registries

There are 11 regional cancer registries in the UK which provide a standard set of data for the Office for National Statistics (ONS) in England and its equivalents in Wales, Scotland and Northern Ireland. There is also an Irish National Cancer Registry which began registering cancers in 1994. Registries provide information for estimating cancer incidence, assessing the outcome of screening programmes and treatments and monitoring of national health policies aimed at improving patient care and survival. Although treated by oncologists, LCH is not a mandatory registerable condition (due to the fact that not all forms of disease are recognised as a malignancy) and cases have not been collected consistently by all cancer registries in the UK [30]. Cancer registries in other countries also vary in their registration of LCH cases. For example, the Pediatric

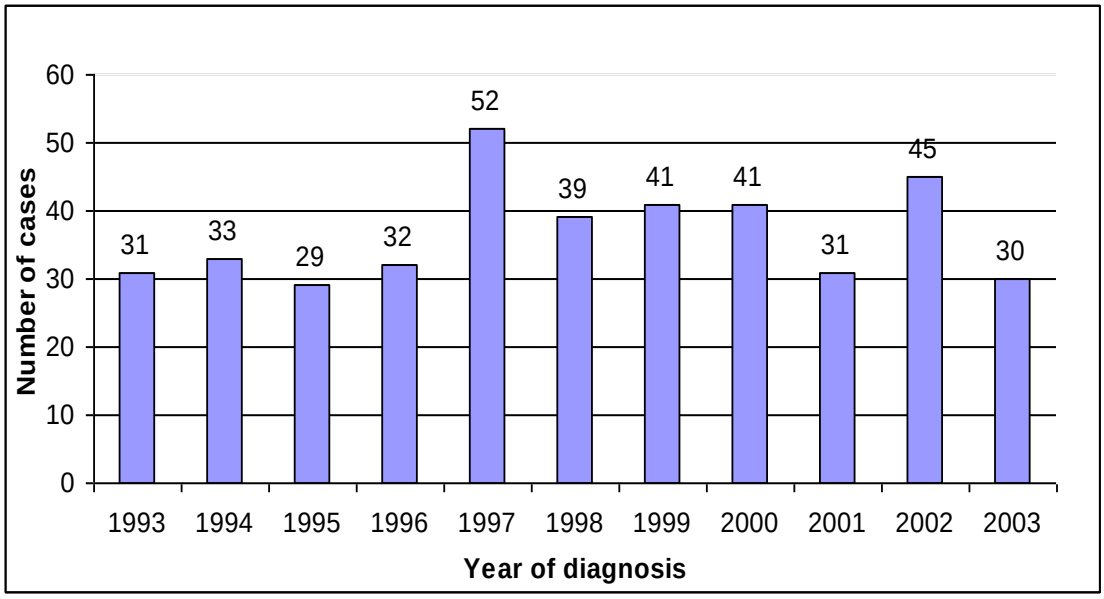
Oncology Group of Ontario registers cases but the Ontario Cancer Registry does not [31].

With regard to sources of information in the UK there is a national children's cancer registry and there are several regional children's cancer registries. Children's cancer registries are believed to be more accurate and up-to-date than general cancer registries as there are fewer delays in registrations, more accurate data capture and more complete ascertainment; most carry out pathological reviews of cases [32]. However, there is only published data on the incidence of LCH from three regional children's registries although a fourth has reported the number of cases registered [2, 21, 25, 33] – see section 2.3.2. Cases ascertained by the National Registry of Childhood Tumours (NRCT) have been mainly via the Children's Cancer and Leukaemia Group (CCLG) with very few additional cases notified by regional and national cancer registries in recent years [30]. The NRCT does not engage in active case-finding. Numbers of cases have been included in their annual report but LCH has not been included in NRCT incidence and survival statistics because many cases are non-malignant and registration was thought to be incomplete. In addition, the NRCT only registers LCH cases up to the age of 15 years and it was of interest to investigate the upper age range for LCH in children.

1.5.3 Children's Cancer and Leukaemia Group (CCLG)

The CCLG co-ordinates clinical trials for all the major types of childhood cancers and LCH, and estimates that it registers 90-95% of all cases [34, 35]. In particular, cases of LCH requiring therapy (multifocal bone and multi-system cases) should be registered. However, those needing little treatment, for example, uncomplicated bone disease, may not have been registered. Children diagnosed before their 15th birthday are included in clinical trials although since registration has been extended up to 24 years, the upper limit for some tumours may be higher [36]. However, referral patterns vary between the 22 paediatric oncology treatment centres and some register few older children [21, 34]. The total number of cases recorded between 1993 and 2003 is shown in figure 1.4. The average number of cases per year over this eleven-year period was 37. The numbers include those notified by clinicians in the Republic of Ireland since Dublin is one of the CCLG treatment centres.

Figure 1.3 CCLG LCH registrations in the UK and Ireland 1993-2003



1.5.4 Death registrations

Death registrations are available from the General Registry Offices at the Office for National Statistics in the UK and Central Statistics Office in the Republic of Ireland [37, 38]. The causes of deaths registered are coded using ICD coding systems (ICD-9 and ICD-10). Searches for deaths from LCH using the appropriate codes may therefore identify cases. However, there is potential for miscoding where histological type codes have not been used. A death may also be misreported since disorders other than LCH may be classified in the group of "Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism".

1.5.5 British Paediatric Surveillance Unit (BPSU)

The BPSU undertakes active (prospective) national surveys of rare conditions affecting children by contacting paediatric consultant members of the Royal College of Paediatrics and Child Health (RCPCH) [39]. The BPSU had previously undertaken a survey of another histiocytic disorder (haemophagocytic lymphohistiocytosis (HLH)) in 1991, for a period of three years, and use of the same method was therefore attractive. LCH fulfilled the criteria for participation in their surveillance programme as it was thought to have an incidence of less than 300 cases per year (based on CCLG numbers and other European incidence rates); the majority of cases would be seen by a paediatrician and it is diagnosed by a definitive method (section 1.4). However, it is a requirement of the BPSU that other

sources should be used when participating in one of their surveys, particularly when investigating incidence. Although the CCLG may be one of the sources, cases would be contributed mainly by paediatricians, many of whom would be members of the RCPCH. Other sources were therefore desirable. BPSU does not undertake surveillance studies solely for the purposes of establishing the incidence of a disease, and consideration was also given to the data that could be collected.

1.5.6 Other potential sources

Other sources used for epidemiological (incidence) studies in the UK include Hospital Episode Statistics (HES), the General Practice Research Databases (GPRD) and the Doctors' Independent Network (DIN) [40-42]. The GP databases record face-to-face contacts and are patient-oriented; HES records episodes of hospitalisation and was not designed to count the number of individuals treated. Patients with particular conditions can be identified by ICD codes and incidences of various conditions have been reported [42, 43]. Although data are anonymised it is possible to identify individual cases. However, data manipulation would be time-consuming. In addition, GP databases would not give complete UK coverage and would be inappropriate given the rarity of LCH. There may also be a delay in the diagnosis of LCH being registered on GP databases, while HES only records those treated as in-patients.

1.6. Types of epidemiological study

The main uses of epidemiological studies in medicine have been to investigate the distribution, causes and natural history of diseases in the population with the aim of controlling and preventing disease, and providing information for health services. Experimental studies (interventional) largely measure the effects of preventative treatments; observational studies (descriptive and analytic) may describe the occurrence of disease in a population or cohort, explain the pattern of disease and identify causal or other risk factors. Descriptive studies usually involve estimating incidence, prevalence and mortality rates in a population, and examining patterns of disease by different subgroups, for example, sex, age or ethnicity. Observations linking the disease to basic characteristics in a population are valuable in informing clinicians of those most at risk of disease and in health service planning. Analytic studies further examine the relationship between health status and particular variables, i.e. investigate risk factors for a

disease, although the two types of study may overlap. As well as describing symptoms, characteristics and natural history, an observational study of LCH may also provide clues to the aetiology of disease.

Data for an observational epidemiological study may be collected retrospectively or prospectively. Prospective studies collect case data after the investigation has started and retrospective studies use cases recorded prior to the study starting. A combination of both methods of collection may be used [44]. Retrospective studies may be quicker to carry out than prospective ones. However, diagnosis or classification of the disease may have changed in the interim and case notes made in the past may be unreliable or unsuitable for the current study. The main advantage of prospective studies (such as those employed via the BPSU) is that the method of recording cases can be controlled from the outset rather than relying on data collected previously for other purposes. A major disadvantage is that they may take many years to collect cases and produce results, especially if the disease is rare.

1.7 A national survey of LCH

1.7.1 Approach and methods

In order to estimate the incidence of LCH and to identify sufficient numbers of cases to obtain meaningful data, a national study was required. The estimates of completeness of ascertainment described above lead to the conclusion that no individual source was likely to identify all LCH cases and that multiple sources of data would be required to ascertain as many as possible. A publication on the National Register of Childhood Tumours (NRCT) reported that cases were ascertained using four sources of notifications including children's cancer registries, clinical trials data and death certificates [18]. The importance of using multiple sources, particularly for rare diseases, has been discussed by Knowles et al. They described the reporting sources of 59/71 studies of rare paediatric disorders conducted through the BPSU [45]. They found that 38 studies used additional sources of ascertainment which they concluded were essential to improve ascertainment, to define the denominator for the study and to assess the level of ascertainment in order to adjust incidence.

Although UK and Republic of Ireland (RoI) cancer registries do not record cases of LCH consistently, the CCLG has registered cases from both countries for many years. However, most of these cases have been reported by paediatric oncologists and it is possible that only more severe cases will have been notified. In addition, only cases up to the age of 15 years may have been registered. Therefore although many cases will have been recorded by the CCLG it is likely that not all will have been registered. This is corroborated by CCLG's own assessment of their ascertainment of LCH and cancer cases (90-95%) [34, 35].

As described, the heterogeneity of LCH makes it challenging to diagnose and treat. The wide range of organs affected, and age at diagnosis, may mean that clinicians from a number of specialties other than oncology are involved and identification of cases on a national scale may also be challenging. In addition to cases registered by CCLG, active methods of ascertaining cases were considered, to cover as many relevant clinical specialties as possible. The BPSU was thus approached to include LCH in its surveillance programme.

To fulfil BPSU participation criteria and complement the BPSU survey and CCLG register, a survey of non-members of the RCPCH was devised. This aimed to include those involved in diagnosing cases – pathologists and radiologists – and those who may treat less severe cases – orthopaedic surgeons and dermatologists – who would not necessarily register patients with the CCLG.

For completeness of ascertainment, a fourth source – death registrations – was included in the study methods.

1.7.2 Summary

Taking into account the different forms of the disease and presentation to different specialists, the limitations of CCLG registration, cancer and deaths registry data, BPSU requirements and human and financial resources, a national survey was designed to establish the incidence of LCH. A prospective study was carried out to actively identify cases via as wide a range of clinicians and specialists as possible using four sources of ascertainment: BPSU, CCLG, death registrations and a survey carried out from Newcastle of non-members of RCPCH. The methods employed are described in detail

in Chapter 3. As well as assessing incidence, the study collected data from questionnaires sent to reporting clinicians, with the aim of describing the disease and looking for evidence of possible causal and other risk factors. In addition, since the disease may result in permanent consequences, patterns of presentation, treatment and outcome were analysed.

1.8 Objectives

The aims of this study as set out in the protocol were to describe the epidemiology of LCH in children in the UK and RoI, to assess the presenting features and referral patterns for the disease and eventually to contribute to a wider investigation also involving Canada and the Netherlands. A study in Canada began in 2009 [46].

1) In particular the study aimed to
    a) describe the incidence of LCH in boys and girls by age and the extent of disease at diagnosis,
    b) study variation between ethnic groups
    c) describe regional differences in incidence rate to assess geographic variation e.g. north/south or urban/rural. (There would be too few cases and too short a timescale of ascertainment for cluster analysis.)
    d) assess the frequency of familial LCH.

2) It also aimed to
    a) document patterns of presentation,
    b) describe the interval between the onset of symptoms and diagnosis,
    c) describe the treatment and outcome for the disease.

In carrying out a national survey among paediatricians it was also hoped to publicise the disease and to increase the index of suspicion in those who might see children with LCH.

1.9 Author's contribution

Discussion and preparations for the study began as early as 2001 although my participation did not begin until the end of 2002. I became fully involved at the time a

second-phase application was being made to the British Paediatric Surveillance Unit (BPSU) to include LCH in their programme. The Histiocytosis Research Trust agreed to fund the study. Following acceptance of the study by the BPSU, I was involved in the preparation of the protocol, study questionnaires and accompanying documentation for clinicians, and the compilation of the mailing lists. I prepared and obtained multi-centre research ethical approval and subsequently, approval for a further follow-up of cases (two years after diagnosis) plus approvals from the CCLG and national statistics offices for data.

Since that time I have run the study on a day-to-day basis, prepared annual and quarterly reports for the BPSU and kept the funders up-to-date. Poster and oral presentations have been made at several conferences including international meetings of the Histiocyte Society. A paper based on this study, of which I am first author, was published in 2009 [47]. Other LCH publications include abstracts written for Histiocyte Society Meetings, a 'Highlight' of another national LCH epidemiology study and a contribution to a paper on adults with LCH [48-52]. A separate list of publications can be found after the Appendixes. In addition, I have become a member of the Histiocyte Society and have attended meetings of the Epidemiology Sub-committee and, when appropriate, meetings of the CCLG LCH Sub-committee.

1.10 Outline of this thesis

The following chapter summarises what is known about LCH from a review of the literature on studies of its clinical characteristics and epidemiology.

Chapter 3 describes the sources and methods used to identify LCH cases in this study and the questionnaires used. Methods used to analyse the data collected can be found in Chapter 4.

Results of case ascertainment, the incidence of LCH and capture-recapture analysis are presented in Chapter 5. Chapter 6 begins with descriptive epidemiology of cases followed by disease-free and sequelae-free survival analysis of one and two year follow-up data, and mortality.

Finally, the study is discussed and evaluated in Chapter 7; recommendations for future studies and conclusions are made in Chapter 8.

Chapter 2. Literature review

A literature review was carried out before the study commenced and was subsequently extended. The literature research strategy is described in Appendix B; search terms included all named forms of the disease mentioned in the Introduction. This chapter gives a detailed description of the features of LCH for comparison with the study cohort and outlines past UK and RoI studies. It also reviews national and regional reports of LCH incidence by age, sex and type of disease. Aetiological studies are described, as are studies of potential risk factors for the development of the disease and associations with other conditions. Mortality and survival studies are reviewed including risk factors for survival and permanent consequences.

2.1 Description of disease

2.1.1 Symptoms and presentation

LCH can occur at all ages [53-55]. The peak in incidence in children occurs between one and four years of age and it is slightly more common in boys than girls [1, 26, 56]. LCH may occur in a single organ (single system disease (SS)) in one or more locations (unifocal or multifocal). Multi-system disease (MS), which refers to LCH in at least two different organs, is more common in children under two years of age. Multifocal SS disease usually affects two to five year olds while 50% of unifocal bone disease affects children over five years old [57]. The variously reported incidence of the disease by age, sex and type is detailed in section 2.3.

Almost any part of the body may be affected and a summary of the main sites is given in table 2.1. SS disease is more common than MS disease and occurs in around 60% of cases, predominantly in bone, skin and lymph nodes [3, 58]. Bone is by far the most frequently reported site of disease and it is estimated to occur in over 70% of cases of LCH [3, 59, 60]. Bone disease may occur at one or more sites and in combination with LCH in other organs. Approximately 15-30% of bone cases are multifocal and it has been found in over 50% of those with MS disease [3, 59, 61]. Almost any bone may be affected, particularly the long bones and skull, although lesions in the extremities are rare [57]. Figure 2.1 shows an X-ray of bone lesions of the humerus. Skull lesions, more

common in younger children, may also affect the eyes, ears or teeth [62]. The main symptoms are pain, limp and swelling or lumps. However, in a study in Dublin, 6/22 cases of SS bone disease were found incidentally [23]. Painful swellings may be mistaken for trauma [63]. SS bone involvement is most frequently seen in older children whose skeletons are still growing, and is more common in boys [64-66]. This may be due to pubertal growth starting later in boys and continuing longer than in girls.

Table 2.1 Main sites of disease

Site	Description
Bone	Although any bone may be affected the skull, femur, tibia and fibula, and spine, pelvis, mandible and ribs are most often involved.
Skin	It occurs as SS disease and is more prevalent in MS disease.
Ears, lymph nodes, thymus	These sites are often associated with neighbouring skin or bone disease.
Lungs, liver, spleen, bone marrow	These (risk) organs are usually only affected in MS disease (disseminated disease).
Endocrine system (pituitary)	Diabetes insipidus (DI) is the most common presentation of pituitary disease and it may occur singly, with or after other lesions, most commonly of the skull.
Central nervous system (CNS)	Apart from the pituitary, all other parts of the CNS may be affected, the cerebellum being the second most affected site.
Gastrointestinal tract	The mouth or gut may be affected and it is more frequent as part of MS disease.

The skin is also commonly affected. It is estimated to occur in 10% of those with SS disease and in over 50% of those with MS disease [67-69]. The first symptoms of LCH may be a skin rash which is seen in up to 50% of cases [67, 68]. Young children are most often affected. Lau et al found that 22/26 cases with skin disease were under 12 months old at the onset, and progression to MS disease occurred in 40% of cases [68]. One form of skin LCH is congenital Hashimoto-Pritzker disease which mainly occurs in early life, regresses spontaneously within 1-3 months and is generally described as self-healing [53, 70, 71]. However, some cases of skin-only LCH have been found to regress initially and recur in the same site or progress to other organs, sometimes several years later. In a study by Minkov et al, the disease progressed in 4/9 non-treated

neonates with cutaneous disease [54]. Stein et al described 19 neonates presenting with skin lesions, 18 of whom were diagnosed with LCH by skin biopsy at a mean age of 3.5 months. At diagnosis a comprehensive workup of each patient was carried out and multi-organ involvement was found in 14 cases. At follow up (mean 3.2 years after diagnosis) two patients had died and 12/19 had MS disease, four patients having developed DI between 2-3 years of age [72]. Given that the course of skin disease may be unpredictable authors have advised careful assessment of patients for systemic disease and monitoring for disease progression [70, 72]. Typical skin lesions described by Stein et al were red and pustular and often crusted although morphological traits varied and could not be used to predict the course of the disease. Rashes may be mistaken for common conditions such as eczema, dermatitis, nappy rash or prolonged 'cradle cap' (figure 2.2) and thus a diagnosis of LCH may be missed [63, 72].

Other organs are affected less frequently affected in SS disease.

In MS disease the most common sites are bone, skin and pituitary [61, 73]. The liver, spleen, lungs and bone marrow are referred to as 'risk organs' because they are associated with a poorer prognosis, especially in infants – see section 2.1.4 [74]. Symptoms of MS disease include rash, jaundice, ear discharge, diabetes insipidus and lymphadenopathy.

Symptom-less or spontaneously regressing bone disease and mild forms of skin disease may go unreported or undiagnosed. It is thought that gastrointestinal disease may also be underestimated since symptoms, such as failure to thrive and diarrhoea, are nonspecific [63, 75].

Figure 2.1 Plain X-ray of lytic bone lesion

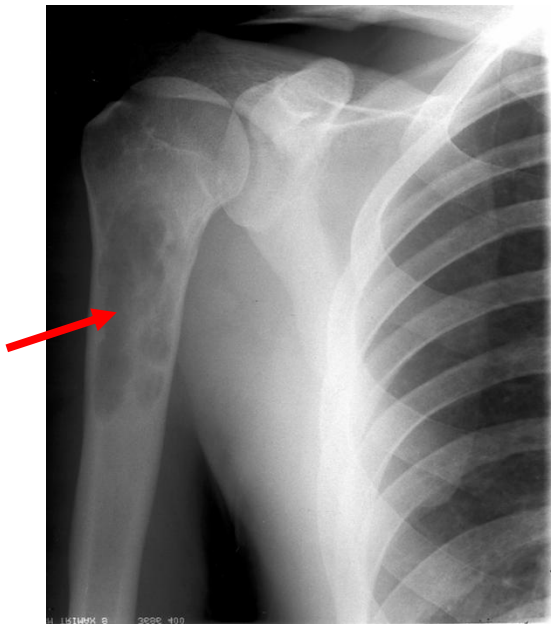
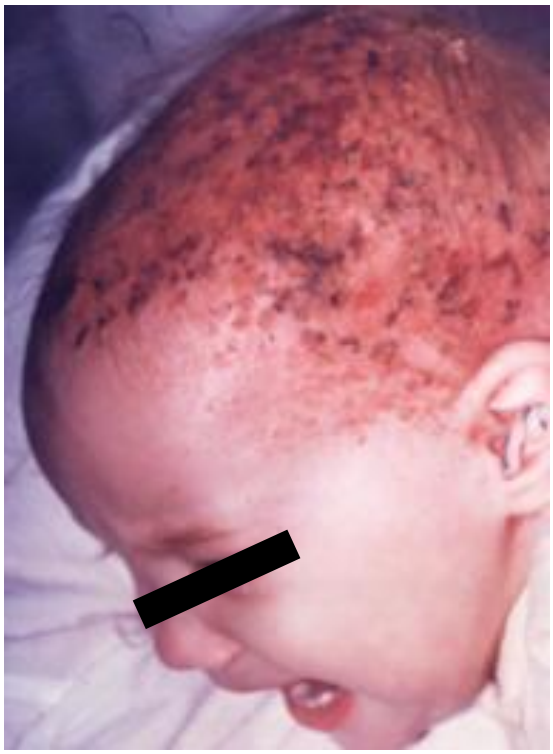


Figure 2.2 LCH presenting as ‘cradle cap’



Both images from Nanduri 2002 [63]

2.1.2 Adults

Although some cases may be referred from childhood, adult cases of LCH are also diagnosed. Adults tend to be treated by an individual specialist, e.g. a dermatologist or respiratory specialist, rather than an LCH specialist, and therefore the incidence has been more difficult to estimate. There have been a few large studies of hospital series but adult disease may be more common than was previously thought. The incidence of LCH in adults is discussed in more detail in section 2.3.4. The most common sites of LCH differ in adults and children. Genital disease (mainly vulval disease) and isolated pulmonary LCH, which are rare in children, are frequent sites in adults [76]. The aetiology of pulmonary LCH is associated with smoking and is discussed further in section 2.4. In adults, lung disease is a major risk factor for both morbidity and mortality; patients are more likely to have a comorbidity such as lymphoma or lung cancer [77, 78].

The different sites in adults and children, and their frequency, where published, are shown in table 2.2. The various sources of frequency of site involvement in children are referenced in the second column. All the frequencies of site involvement in adults (shown in the fourth column) are taken from two papers by Arico et al and Howarth et al [55, 76]. Frequencies from Howarth et al are marked with †. As can be seen, there is a very wide range in pituitary LCH reported by Grois et al [73].

Arico et al reported that 68% of 274 adults aged over 18 years in the International Histiocyte Society Adult Registry had MS disease. Of those with SS LCH, over 50% had lung disease with 38% having bone and 7% having skin disease; the frequencies were much higher in MS disease cases (61%, 66% and 50% respectively) [76]. The numbers with isolated lung disease were slightly lower (40%) in a US study by Howarth et al and 22% in a report from the LCH-Belgian Survey [44, 55]. In another US adult group of 211 orthopaedic cases, Islinger reported that 75% were male [79]. Although smoking is more prevalent in men [80] the reported frequency of pulmonary LCH among men and women varies. In a review by Vassallo et al, some studies reported a male predominance although more recent studies reported an equal incidence or slight predominance among women. The authors suggested that this may reflect the "increased prevalence of smoking among women in recent years" [81]. The ratio of males to females with pulmonary disease in Howarth's study was 1:2.2. In the German

National Database of Adult LCH Patients, data on 121 adults (35% male, 65% female) were collected between 2002-2008. Patients had a mean age of 44 years at diagnosis and 86% were smokers or ex-smokers [77].

Table 2.2 Most common sites of LCH in children and adults with frequency, where reported (adapted from Tatevossian [55])

Children	Frequency
Bone	70-80% [59, 82]
Skin	10% SS [83], 50% MS [68]
Ears, Nose Throat	>15% [84]
Pituitary	5-50% [73]
Orbits	Up to 20% [85]
Mouth	6% [86]
Gastrointestinal tract	2-13% [87]
Lungs	<5% SS [61] 12% MS [56]
Liver	4% [82]
Spleen	
Lymph nodes	<10% [82]
Thyroid	
Other rare sites	

Adults	Frequency
Lungs	51% SS, 61% MS 40% SS, 43% MS†
Bone	38% SS, 66% MS 52% SS, 77% MS†
Skin and muco-cutaneous junctions	7% SS, 50% MS 6% SS, 65% MS†
Pituitary	43% MS 0.9% SS, 44% MS†
Dental	
Genital (mainly vulval)	
Liver	1.2% SS, 23% MS 5% MS†
Spleen	
Thyroid	9% MS
Other rare sites	

All adult figures from Arico et al [76], and Howarth et al† [55]

2.1.3 Time from symptoms to diagnosis

Since the early stages of the disease are variable and milder forms may be mistaken for other disorders there may be a long delay between the first symptoms and diagnosis. Lack of timely treatment may allow the disease to progress and increase the possibility of permanent consequences. Stein et al in a study of 19 neonatal cases of cutaneous

LCH reported misdiagnoses such as psoriasis and dermatitis prior to presentation at their hospital in Chicago. Over 70% of cases had skin lesions at birth but the mean age at diagnosis was 3.5 months (range 2 days to 20 months) [72]. More recently one national study has estimated the elapsed time between symptoms and diagnosis for 352 children aged <15 years, diagnosed in France over a six year period [88]. For SS (unifocal) LCH the median time from symptoms to diagnosis was 33 days increasing from 30 days for bone to 77 days for skin and 119 days for endocrine disease. For those with multifocal or MS disease the median elapsed time was 48 days.

2.1.4 Treatment

Treatment depends on the site of disease and, if MS, whether children are at risk of dying. Those with two or more organs including a risk organ – liver, lung, spleen or bone marrow – are most at risk [89]. Surgery or chemotherapy may be required but since the disease may regress spontaneously for many patients treatment is simply 'waiting and seeing'. Conservative treatment has been advocated and, in a recent French study of 258 children, 43% underwent observation only [3, 90]. Radiotherapy is now avoided because of its possible role in the subsequent development of malignancies in these patients – see section 2.5.5 [91].

For many years children have been treated on internationally agreed protocols developed by the Histiocyte Society, based on classification of the type of disease [74]. Clinical trials of these treatments have been conducted in the UK and Ireland under the auspices of the CCLG. In the French study, mentioned above, Guyot et al reported that 36% of children had been treated on LCH II or LCH III protocols [3]. The criteria for eligibility for current treatment (on LCH III protocol) are given below (table 2.3). A new protocol (LCH IV) is in the process of being established based on the results of previous clinical trials. It has been reported, that lung, if the only risk organ involved, does not confer a higher risk of death and it will be removed from the list of risk organs in future studies [92].

Unfortunately, owing to the rarity of LCH and the current nature of EU regulations for new clinical trials in children, it is possible that UK patients will not be able to be entered into the upcoming LCH IV study [93]. Clinical trials units may have to reduce the number of trials they can offer as increasing amounts of time and resources are

being taken up by audits and the requirements of the EU Clinical Trials Directive. Other recent changes have meant that children's cancer and LCH trials are no longer being conducted by CCLG at Leicester University. However, much of the CCLG's work is being transferred to Birmingham Clinical Trials Unit.

Table 2.3 Treatment - LCH III protocol eligibility [74]

Protocol group	Eligibility – site of disease
Group 1 - MS "risk" patients	MS patients with involvement of one or more "RISK" organs i.e. hematopoietic system (with or without bone marrow involvement), liver, spleen or lungs Patients with SS lung involvement are not eligible for randomisation
Group 2 - MS "low risk" patients	MS patients with multiple organs involved but WITHOUT involvement of "RISK" organs.
Group 3 - SS "multifocal bone disease" and localised "special site" involvement	Patients with multifocal bone disease, i.e. lesions in two or more different bones. Patients with localised special site involvement, like "CNS-RISK" lesions with intracranial soft tissue extension or vertebral lesions with intraspinal soft tissue extension *(CNS RISK" lesions - lesions in the orbital, temporal/mastoid, sphenoidal, zygomatical, ethmoidal bones, maxilla, sinuses or anterior or middle cranial fossa, with intracranial soft tissue extension demonstrated on magnetic resonance imaging (MRI). Vault lesions are not regarded as "CNS Risk" lesions.)*

2.1.5 Reactivation and progression

The disease may recur or reactivate after treatment, particularly in those with MS disease, sometimes many years after diagnosis [56, 94-97]. It may reactivate at the original site of disease or progress to new sites. For example, SS bone disease may reactivate at the original site or become multi-focal, or may progress to MS disease; disease in MS cases previously at low risk may progress to risk organs. In a study of 300 children in Buenos Aires, LCH recurred in 30% of cases overall – 21% of cases of SS disease and 48% of those with MS disease [96]. The proportion of cases with

recurrence reported by Jubran et al in a study of 122 cases was 17% and 50% for SS and MS disease respectively [94]. In a study using data from the International LCH Registry, of 335 MS patients, complete resolution of disease was documented in 64% of cases after a median observation time of 1.5 years. However, reactivation occurred in 134 cases (40%), mostly within two years of disease resolution (88%). The probability of first reactivation was 46%, and 44% for a second reactivation at five years after disease resolution. The most frequent site of first reactivation was of the skeleton with only 10% of recurrence in risk organs. The extent of reactivated disease did not match the extent of disease at diagnosis except where risk organs were involved. The number of reactivations per patient ranged from 1-6 with the vast majority of survivors having only one or two [98]. In a long-term follow up study of 40 cases in Stockholm, 18% had reactivated disease 10 years after diagnosis. The disease progressed in 12 cases; six cases of unifocal SS disease developed multifocal or MS disease and in six cases of MS disease it progressed to risk organs [97].

2.1.6 Permanent consequences

Since LCH may affect several organs, sequelae or permanent consequences may follow or be concurrent with active disease [63, 95, 99]. Children are thought to be at particular risk of developing long-term sequelae from LCH because the disease may interfere with normal growth and development. The main permanent consequences and their estimated frequencies are shown in table 2.4. The reported sites vary quite considerably with wide ranges in the percentages of cases. This may be due to various factors including the study size, treatments used and follow-up period. The most common permanent consequences are orthopaedic problems and diabetes insipidus [96, 100]. In a study by Willis et al, among 71 cases with a median follow up of 8.1 years, 42% had skeletal problems and 25% had diabetes insipidus. In contrast, the proportions of cases with these sequelae in a multi-centre study in France (with a median follow up of 3.3 years) were 2.5% and 17.5% respectively [56].

In a study of 123 cases with a median follow-up of three years, Braier et al reported sequelae in 28% of cases [95]. In the long-term follow up study (5.5-33.5 years after diagnosis) in Stockholm mentioned above, the proportion of cases with sequelae was higher (42%) [97]. This may be due to there being a longer period in this study in which the disease progressed and sequelae developed. In children with SS LCH

(usually bone or skin) the outcome is frequently very good. The disease may regress spontaneously or a complete recovery may be made with conservative treatment. However, of 178 cases with SS disease in a multi-institutional study in Europe, 25% had permanent consequences [58]. For those with MS disease, the proportion may be higher and in two studies by Willis et al and Haupt et al, 64% and 71% of cases respectively were left with significant permanent consequences after more than three years of follow up [101, 102].

The effects of multiple LCH lesions of the skull after diagnosis and treatment are shown in figure 2.3 [63]. Risk factors for the development of permanent consequences are described in section 2.6.2.

Table 2.4 Main permanent consequences of LCH (adapted from Haupt et al) [99]

LCH	Permanent consequences	Frequency in LCH patients
Bone	Orthopaedic problems – deformities, scoliosis, facial asymmetry	2.5-42%
Posterior pituitary	Diabetes insipidus	15-50%
Anterior Pituitary, hypothalamus	Growth failure – short stature, Hormone deficiencies – delayed puberty, obesity	Up to 20%
Central nervous system	Learning difficulties, psychological problems, ataxia, gait disturbances, tremor	Up to 10%
Orbits	Ophthalmic problems, proptosis (rarely blindness)	Not reported
Ears	Hearing loss	3-16%
Dental	Tooth loss	1-30%
Liver	Chronic liver disease e.g. sclerosing cholangitis, cirrhosis	1.3%[&],18%[#]
Lung	Restrictive lung disease, fibrosis, pneumothorax	1-8%

Estimates from [&][56], [#][103]

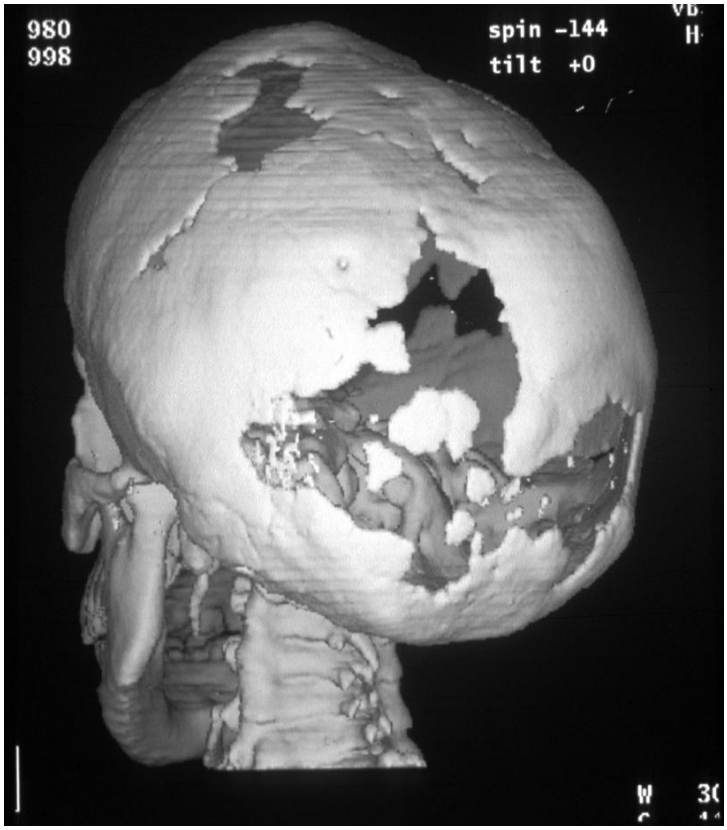
2.1.7 Survival

Several long-term follow up studies have been reported and children with MS disease involving risk organs have the poorest outcome in terms of survival as well as permanent consequences [97, 101, 102, 104]. Although children under two years old at

diagnosis are thought to be particularly at risk, Jubran et al reported a significantly higher risk of progression of disease or death in infants with MS disease aged less than one year old at diagnosis [94]. Similarly, in a multi-centre study in France of 348 cases between 1983-1993, the median age at diagnosis of those who died was 8.5 months (range 0 months to 11 years) [56].

Mortality and survival rates are described in section 2.6.

Figure 2.3 3D CT scan of skull



Persistent, multiple, large lytic lesions with 'full-thickness' loss of bone, 15 years after initial diagnosis of LCH and 8 years from the end of treatment. (From Nanduri 2002)[63]

2.2 UK and Republic of Ireland studies

UK and Irish clinicians have contributed to a wide range of publications on LCH [62, 105, 106]. However, there have been few reports from large hospital series. Studies in

the UK and Ireland include case reports, clinical features, specific organ disease, and reviews of treatment, outcome and quality of life. A list of studies with the largest patient groups is shown in table 2.5.

Cases were mainly from hospital series although one study obtained cases from the Scottish Bone Tumour Registry [107]. As can be seen in table 2.5, the number of cases varied between studies. Over a 31-year period in Dublin (1959-1989) an average of 1.3 patients per year were diagnosed while at Great Ormond Street Hospital (GOSH), over a 26-year period (1957-1982), there was an average of three patients per year [23, 108]. The difference may simply reflect the larger population served by GOSH. In later years (1980-1987), 58 patients were seen at GOSH – an average 7.2 per annum [90]. However, this series appears to overlap with another in a study of children with lung involvement in which 61 cases of LCH were examined (1981-1987) [109]. In the second (lung) study, 10/61 cases were referred from outside the UK so the increase in average numbers may be due in part to non-UK resident referrals rather than more prevalent disease or better recognition and diagnosis. The 51 UK residents were mainly boys (70%). One study which identified cases from the Scottish Bone Tumour Registry reported similar numbers of children (39) and adults (31) with bone LCH [107].

A follow up study of patients at GOSH with MS LCH was carried out by Nanduri et al in 2006 [110]. They identified a subset of patients from 275 cases seen between 1966 and 1998 of which 147 (53.5%) had MS disease. This is a higher proportion of MS cases than that seen in the Dublin study (46%) and elsewhere where the majority of cases are of SS disease [56, 58]. This may be accounted for by the fact that GOSH is a tertiary paediatric centre and national children's hospital, and more numerous complex cases may be referred there. There were 36 deaths at GOSH (13%) and eight (21%) in Dublin over 34 years and 31 years respectively.

With regard to the frequency of organ involvement, data from several GOSH studies are available. In a study over 26 years, 18/76 (23%) had ophthalmic LCH. However, (unspecified) changes in referral patterns had meant that half the cases presented in the last six years [108]. From a total of 275 cases diagnosed between 1966-1998, endocrine disorders were found in 35% of 144 patients with MS disease, and 34% had diabetes insipidus [111]. In the same series, five cases (1.8% of all patients and 3.3% of those

with MS disease) had colon involvement; the median age at diagnosis was 0.6 years [87]. Ear involvement was also investigated; 58 cases (21%) had ear disease although a more recent study of 40 MS cases found that 70% had had ear involvement and, five years on, 38% suffered from hearing loss [112]. Head and neck were involved in 82/131 (62%) cases treated over a 30-year period at Cambridge and GOSH, and, of these, 44 (34%) presented with SS disease. The most common site was skull vault followed by skin of the ear canal. A further 14 children developed head and neck lesions [86].

In an earlier series, of 61 patients diagnosed with LCH between 1981-1987, 45 had MS disease and 16 had SS disease [109]. Lung involvement was found in 42% of MS cases and in none of the SS cases which is similar to another report from Philadephia [113]. Lung disease was most common in the youngest patients; the median age was 0.6 years. The frequency of various sites of disease may not be typical from UK accounts since nearly all the studies have been carried out at GOSH where a large proportion of MS cases were seen.

Recurrence and progression of bone disease in children and adults was compared in Scotland in 39 and 31 cases aged under and over 16 years respectively [107]. In the younger age group, 17% had recurrence of disease including additional sites; in the skeletally mature group, 12% had reactivation of bone disease only. The authors concluded that the outcome for paediatric patients with SS bone disease was less good than previously reported. Long-term morbidity and health-related quality of life have been reported in several studies by Nanduri et al [63, 110, 114]. In a cohort of 40 cases with MS disease, almost half had moderate to severe sequelae and ten had psychological, learning or physical problems which affected their independence. They concluded that regular follow-ups would help to identify early signs of sequelae and to make appropriate interventions.

None of the UK studies was population based. Three regional children's cancer registries in the Northeast, Northwest and West Midlands have published incidence rates for LCH and one other in the Southwest has reported the number of cases registered [2, 21, 25, 33]. These are described in section 2.3.2.

Table 2.5 Studies in the UK and Republic of Ireland

Title	Patient population	Number and age of cases at diagnosis	Time period	Type of disease	M:F ratio	Deaths	Reference
Langerhans Cell Histiocytosis – a 31 year Review (1991)	Hospital series – Dublin	41 <15 yrs	1959-1989	22 UF/MF bone, 19 MS	2.4:1	9	[23]
Langerhans cell histiocytosis and the pediatric population (Abstract 2003)	Hospital series – Dublin	68 - age not stated	Not stated	46 SS, 22 MS	–	6	[115]
Eosinophilic Granuloma in children and adults – the Scottish Experience (Abstract 2006)	Scottish Bone Tumour Registry	39 < 16 yrs, 31 > 16 yrs	Not stated	61 UF, 9 MF	–		[107]
Histiocytosis X: an ophthalmological review	Hospital series – London	76 <12 yrs (18 ophthalmic LCH)	1957-1982	SS and MS	–		[108]
Langerhans cell histiocytosis: the case for conservative treatment (1990)	Hospital series – London	58 <15 yrs	1980-1987	14 SS, 44 MS	2.2:1	8	[90]
Lung involvement in Langerhans Cell Histiocytosis: Prevalence, Clinical features, outcome	Hospital series – London	61 (51 UK residents) <16 yrs	1981-1987	16 SS, 45 MS	2.4:1	7	[109]
Growth and endocrine disorders in multi-system Langerhans cell histiocytosis	Hospital series – London	54/144 (subset) <17 yrs	1966-1998	MS	1.2:1		[111]
Long-term morbidity and health related quality of life after multi-system Langerhans cell histiocytosis	Hospital series – London	40/147 (subset) <16 yrs	1966-1998	MS	1.1:1		[110]
Cognitive outcome of Long-term survivors of langerhans Cell histiocytosis: A single Institution, Cross-sectional Study	Hospital series – London	28/40 (subset) <16 yrs	1966-1998	MS	1.3:1		[114]
Langerhans' cell histiocytosis in childhood: Management of head and neck manifestations	2 centres – London, Cambridge	131 <17 yrs	1960-1991	SS and MS	1.7:1		[86]

2.3 Incidence studies

2.3.1 National studies

It has been estimated that approximately one in 200,000 children are diagnosed each year although evidence for this has been sparse [1, 20]. However, since this study began the incidence of disease has been reported elsewhere [3].

The first national study, published in 1993, which is still quoted in all publications when discussing the incidence of LCH in children, was in Denmark [1]. Only an abstract is available. The authors obtained data retrospectively from 1975-1989 asking relevant clinical departments in hospitals in Denmark to look for all cases of LCH. The list of clinical specialties approached was comprehensive and included Dentistry and Radiology departments. Records were reviewed and biopsies were re-examined for all 90 children under 15 years of age. The incidence rate (IR) was 5.4 per million per year rising to 16.4 per million per year in those with MS disease under the age of two years. The study relied on clinicians reporting cases and although there may have been some under-ascertainment, over-ascertainment is unlikely as biopsies were reviewed to confirm the original diagnoses.

Since the publication of the Danish abstract several studies have reported national incidence rates of LCH and a summary of these and other population-based reports are presented in table 2.6. Although their source was not stated, Lavin and Osband reported that there were approximately 1200 new cases a year in the US, an estimated incidence of 2-5 children per million per year [116, 117]. In addition, for a study on ophthalmic cases, Kramer et al calculated an expected incidence rate for children in Arizona based on the number of cases reported between 1980-1989 to the Surveillance Epidemiology and End Results (SEER) program of the National Cancer Institute [118]. The age-specific IRs reported by SEER ranged from 0.6-4.3 per million per year aged 0-4 years. (The study by Kramer et al is further discussed in section 2.5.4.)

The most recent national study was performed in France with 254 children aged <15 years diagnosed between 2000 and 2004 [3]. The IR was 4.6 per million per year. As can be seen from table 2.6 the national incidence in children from all reports ranges from 1.37 (aged <15 years) in Taiwan to 8.3 per million per year (aged <20 years) in Belgium [44, 119]. The difference in rates may reflect the different methods of

ascertainment, different age groups or underlying differences in the rates in each country or region.

In table 2.6 the age of the study population reported is given in column six; IRs (last column) are for children aged 0-14 years, unless otherwise indicated. Among the national studies, the IR for Hungary is for those aged 0-18 years, and IRs for Belgium are for those aged 0-20 years and adults; a French multi-centre study included cases aged 0-17 years and the estimated IR was for 0-15 year olds. An overall IR was calculated for Taiwan from published case numbers and mid-year population figures for the five-year study period; the annual IRs were 1.37, 1.59, 3.23, 3.29, 1.68 per million per year aged 0-14 years. Among the regional studies, the children's registry in the North of England records cases up to 24 years and the IRs presented are for those aged 0-14 years and 15-24 years; an IR was calculated for Southwest England from a report on children aged up to 16 years; the IR reported by Raney and D'Angio in the US was for cases aged 0-20 years.

Sources included surveys of single specialty clinicians (mainly oncologists and haematologists) cancer registers, and combinations of these and other specialists such as pathologists in the Belgian survey [44]. The 2008 French study was thought to have almost complete ascertainment of cases (97%) using two sources, the French National Registry of Childhood Hematopoietic Malignancies and the French LCH Study Group [3]. In contrast, a Japanese nationwide survey of LCH and Haemophagocytic Syndrome used only one source of cases – paediatric haematologists – with a 60% response rate. The annual number of cases (20.4) was comparable with those registered by the Japan Children's Cancer Registry (22.3). However, since only haematologists were contacted, the authors conceded that some cases treated by orthopaedic clinicians or dermatologists may have been missed [120]. Adjusting to account for the 60% response rate, the estimate of case numbers was 34 cases per year (1.5 per million per year aged <15 years).

In the French study, completeness of ascertainment was calculated using two-source capture-recapture methods which were also used in this study and are described in Chapter 4. Few of the studies listed in table 2.6 gave an estimate of completeness of ascertainment but where published the estimates ranged from 90-97%.

All the studies were carried out retrospectively, with the exception of the Belgian survey which used both retrospective and prospective data [44]. Most studies stated the basis on which cases had been diagnosed. In the Japanese study, the diagnosis was presumptive or not specified for over half the cases; in Taiwan, diagnosis was based on symptoms and histology and 60% of cases were confirmed by immunohistochemistry [119, 120]. In two studies in France, diagnosis was by biopsy or radiological findings for 97% and 98% of cases respectively [3, 56]. Case numbers are likely to be accurate in reports from registries since they collect data from several sources, and patient information may include pathology reports. In addition, many have procedures in place to cross-check and correct anomalies [20, 29].

Table 2.6 Summary of population-based reports of incidence of LCH

National studies							
Authors	**Publication**	**Data Source**	**Period**	**No. of cases**	**Age (years)**	**Sex ratio M:F**	**IR (per million per year) (aged 0-14 years)**
Carstensen & Ornvold [1]	Abstract	National – All Danish paediatric and specialist clinics and departments	1975-89	90	<15	2.2:1	5.4
Kaatsch, Haaf, Michaelis et al [20]	Article	National – German Registry of Childhood Malignancies	1980-1992	488	<15	1.4:1	4.0[1]
Muller, Garami, Hauser et al [27]	Article	National – Hungarian Childhood Cancer Registry	1981-2000	111	<18	1.36:1	2.24 (aged 0-17 years)
French Langerhans Cell Study Group [56]	Article	National – 32/37 French Oncology Centres	1983-93	348	0-17	1.3:1	4.5 (aged 0-15 years)
Imashuku, Ikushimu, Hibi et al [120]	Article	National survey of Japanese Society of Paediatric Haematologists	1986-1990	102	<15	1.6:1	1.5[2]
Chen, Lin, Chang et al [119]	Article	National – 23 Taiwan Pediatric Oncology departments	1995-1999	55	<15	1.5:1	2.22[3]

[1]based on data for 1987-1992 [2]estimate after adjusting for 60% response rate [3]calculated rate

Authors	Publication	Data Source	Period	No. of cases	Age (years)	Sex ratio M:F	IR (per million per year) (aged 0-14 years)
German Childhood Cancer Registry [26]	Registry report (web-pages)	National – Data from German Oncology Clinics and trials	2000-2004	330	<15	1.6:1	6.0 (ASR)[1]
Guyot-Goubin, Donadieu et al [3]	Article	French National Registry of Childhood Haematopoietic Malignancies and French LCH Study Group	2000-2004	258	<15	1.2:1	4.6 5.0 (ASR)[1]
Swiss Childhood Cancer Registry [29]	Article	National and Swiss Paediatric Oncology clinics (9)	2001-2005	24	<15	1.4:1	4.3 (ASR)[1]
Vangeebergen, Van Eycken, Van Gool [44]	Abstract	LCH-Belgian Survey of pathologists/clinicians plus sampling from Belgian Registry	2001-2006	128	All ages	–	8.3 (aged <20 years) 2.2 (adults)
Belgian Cancer Registry [44]		National – Belgian Cancer Registry	2004-2006	53	All ages	1.2;1	3.0 (all ages)

[1]ASR = Age standardized rate

Regional studies							
Authors	**Publication**	**Data Source**	**Period**	**No. of cases**	**Age (years)**	**Sex ratio M:F**	**IR (per million per year) (aged 0-14 years)**
Alston, Tatevossian, McNally et al [2]	Article	Regional Children's Registry – Northwest England	1954-1998	101	<15	1.1:1	2.6 (ASR)[1]
Cotterill, Parker, Malcolm et al [25]	Article	Regional Children's Registry – Northeast England	1968-1995	46	<24	1.15:1	2.5 (ASR)[1] 0.3 (ASR[1] aged 15-24 years)
Muir, Parkes, Mann et al [33]	Article	Regional Children's Registry – West Midlands, England	1980-1984	13	<15	2.3:1	2.2, 3 (ASR)[1]
South West Childhood Cancer Research Registry [21]	Registry Report (web-page)	Regional Registry – Southwest England	2002-2006	16	<16	–	3.4 <16 years[2]
Stalemark, Laurencikas, Karis et al [28]	Article	Regional – Stockholm County, Sweden	1992-2001	29	<15	1.4:1	8.9
Raney and D'Angio [113]	Article	Greater Delaware Valley – referral area for Philadelphia Children's Hospital, US	1970-1984	83	<21	1.4:1	2.0 (age 0-20 years)

[1]ASR = Age standardized rate [2]calculated rate

2.3.2 Regional rates

In the UK, using data from children's cancer registries, regional IRs of LCH for those under 15 years have been published for Northwest England (1954-1998) and the North of England (1968-1995); they were 2.6 and 2.5 per million per year respectively [2, 25]. The West Midlands Regional Children's Tumour Research Group reported 13 cases of Histiocytosis X over a five year period (1980-1984) with a similar IR of 2.2 per million per year [33]. In that publication the IR was compared with those reported by the Northwest region (2.3) and nationally, (0.6) by the Children's Cancer Research Group (which houses the NRCT). The national rate was presumed to be an under-estimate because of poor LCH registration in registries contributing to NRCT. A rate of 3.45 per million aged <16 years has been calculated for the Southwest Region based on the reported numbers of cases between 2002-2006 [21]. However, there may have been some cross boundary referrals; 12% of CCLG (cancer and LCH) registrations from Bristol, the main centre in the Southwest, were from outside the region.

The West Midlands registry estimated that ascertainment was 95% complete. Completeness of ascertainment was 95% for the Northwest and 98% for the North of England children's cancer registries.

In the Danish study it was reported that regional IRs varied only slightly although the actual rates were not published [1]. Similarly, in the Belgian survey there were no major differences between regions in Flanders [44]. In the Greater Delaware Valley in the US, the referral area for Philadelphia Children's Hospital, the IR for those under 21 years between 1970-1984 was just over two cases per million per year [113]. This is comparable with the US estimated rate of 2-5 cases per million per year [116].

A higher rate of 8.9 per million per year has been reported in Stockholm County in a study of 29 cases over 10 years; other regional rates in Sweden are not reported. All children in the county with LCH are referred to a single centre which is advantageous in identifying cases. Ascertainment was considered to be very comprehensive and this may be reflected in the higher incidence compared to those reported in parts of the UK and US [28].

An epidemiological study of histiocytic disorders (LCH, HLH and malignant histiocytosis) was reported in Northeast Egypt from a hospital centre which admits patients from four governorates [121]. Over a five year period 22/27 cases were diagnosed with LCH, all less than 10 years of age. The region has a childhood population of 7 million although the age range was not stated. The childhood incidence of LCH is estimated at approximately 0.6 per million per year. Most of the 27 cases (74%) came from one governorate. This may be because it has the highest population of the four governorates reported or may implicate some environmental factor.

2.3.3 Age

The incidence of childhood LCH decreases with age, the highest rate being in children with MS disease under one year of age. Published rates by age group are reported in table 2.7. In a study in France IRs decreased from 15.3 in children less than one year old to 2.0 per million per year in the 10-14 years age group [3]. Similarly IRs reported by the German Childhood Cancer Registry ranged from 23 per million per year in those aged less than one year to 3.0 per million per year in those aged 10-14 years [26]. The rates in two UK regional studies showed the same trend but were lower in all age groups.

There have been several reports of congenital and neonatal cases. Guyot-Goubin et al reported that 5/14 infant cases identified from French registries were diagnosed under four weeks old [3]. Using data from the German Childhood Cancer Registry, Minkov et al estimated the incidence of neonatal LCH (diagnosed age <28 days) to be 2 per million per year [54]. This may be suggestive of a prenatal origin of the disease [53, 122, 123].

Table 2.7 Reported incidence rates (per million per year) by age group

Author	Place	<1 year	1-4 years	5-9 years	10-14 years
Guyot-Goubin et al [3]	France	15.3	7.2	3.2	2.0
Cancer Registry report [26]	Germany	23	7	4	3
Alston et al [2]	NW, UK	9	4.6	1.1	0.7
Cotterill et al [25]	NE, UK	8	3.2	1.5	1.4

2.3.4 Adults

There have been no population-based studies of LCH in adults and only three studies with over 100 adult cases, one being an international multi-centre study [55, 76, 79]. In a large study at a hospital centre in the US, 58% of 314 patients ranging from 2 months to 83 years were aged over 20 years; the median age at diagnosis was 24.5 years [55]. In a second US study of 541 patients, 39% of cases were aged over 21 years and had a mean age of 32 years [79]. In the international Histiocyte Society Registry of 274 adults (aged over 20 years) from 13 countries, the mean age was 35 years at diagnosis. The peak incidence was in young adults and it decreased with age – 46% were aged <30 years, 32% were 30-44 years, 16% were aged 45-59 and 6% were > 60 years [76].

Estimates of incidence range from 1-2 adults per million to "at least 10-15 per million persons per year" based on a study of lung disease by Colby et al [124, 125]. More recently, between 2001-2006 the LCH-Belgian Survey prospectively registered similar numbers of children (aged 0-20 years) and adults – 67 and 61 cases respectively, giving IRs of 8.3 and 2.2 per million per year. The rates were similar to that for all ages from the Belgian Cancer Registry (3.0 per million per year between 2004-2006) where data had been collected retrospectively [44]. A national database of adult LCH cases is being established in Germany which may eventually confirm these incidence rates [77].

2.3.5 Sex

In most studies a slight male predominance has been reported with a male to female ratio ranging from 1.1 to 2.2 (see table 2.1.1). The reason for this difference is not known. However, the IR in France for boys and girls aged less than 15 years was similar at 4.9 and 4.3 per million per year respectively and Alston et al found no difference in the incidence rate by sex in Northwest England (p=0.81) [2]. The LCH-Belgian Survey registry has a total of 247 children and adult patients registered, of which 56% are male (ratio 1.3:1) [44].

2.3.6 Type of disease

Several studies have published incidence rates by type of disease. Infants and young children have a higher incidence of disseminated disease than older children in whom SS disease is predominant [22]. The incidence in children under two years of age was as high as 16.4 per million per year in Denmark [1]. In France, Guyot-Goubin et al

reported an incidence of 2.6, 1.3 and 0.6 per million per year for children under 15 years with SS (unifocal), MS RO- and MS RO+ disease respectively [3]. In Stockholm County the rates were higher – 6.2 for those with SS disease and 3.3 and 1.2 per million per year for cases with MS RO- and MS RO+ disease respectively [28]. The disease progressed in several children and at its maximal extent (after a median of six years follow up) the incidence was 4.3 for those with MS RO- disease and 1.5 per million per year for those with MS RO+ disease.

Incidence rates by type of disease were broken down further by age group in France as shown in table 2.8 [3]. The highest rate (8.2) was in children aged less than one year with unifocal disease although this age group had the highest rates of all forms of the disease. 77% of these children had skin disease which accounts for the high incidence rate of unifocal disease in this age group. It is generally accepted that unifocal disease occurs mainly in children over five years old, bone being the most common site. Although the IR is low (2.4 per million per year), 93% of children in the 5-9 years age group had bone disease compared with 10% in <1 year, 80% in 1-4 years and 86% in 10-14 years age groups.

In the UK, Alston et al similarly found that skin was the most common site of disease in those under one year of age (76%) [2]. Bone disease occurred in 69% of patients aged 1-4 years (as single or MS disease) and was present in 100% of those aged 5-14 years. The proportion of those with MS disease was 64% aged <1 year, 71% aged 1-4 years and 17% aged 5-14 years.

Table 2.8 Incidence rates (per million per year) in France by age group and type of disease [3]

Age group (years)	Unifocal	MS RO-	MS RO+	Total
<1	8.2	2.4	4.7	15.3
1-4	3.0	3.0	0.9	7.2
5-9	2.4	0.7	0.1	3.2
10-14	1.5	0.3	0.1	2.0

De Filippi et al have suggested that the risk of developing SS as opposed to MS disease may be genetic with "specific cytokine gene variants affecting susceptibility to LCH and its clinical heterogeneity" [126].

2.3.7 Trends over time

There is no evidence that the incidence rate of LCH has changed over the period during which incidence studies have been conducted. The LCH-Belgian Survey reported that incidence remained stable over a six-year period [44]. In the Northwest of England cases diagnosed between 1954-1998 showed a decline in the rate of LCH in children under one year of age from 10.9 per million per year in the early years to 6.1 per million per year in the latter years. However, the overall incidence rate for children under 15 years remained fairly constant over the diagnostic time period with a rate of 2.6 per million per year. This study also reported an increase in the diagnosis of bone and soft tissue disease and a decrease in liver and lung lesions over time. Better diagnostic techniques may account for the increased identification of cases [2].

2.4 Aetiology

The cause of LCH remains unknown except for isolated pulmonary disease in adults which is strongly associated with smoking; the majority of patients with the disease are smokers or ex-smokers [55]. The association is supported by mouse models in which exposure to tobacco smoke induced inflammation similar to pulmonary LCH in humans and which regressed when the exposure stopped [81]. Isolated lung disease in children is rare and its origins are unknown but smoking has been thought to be causal in a few reports including a child who had smoked for two years and in a toddler exposed to passive smoking [127, 128]. Bernstrand et al followed up 41 LCH cases (34 children and 7 adults) more than five years after diagnosis and 7/10 with radiographic abnormalities were smokers. 7/10 of these cases had had lung involvement at diagnosis although only 2/10 had any respiratory symptoms at follow up. Numbers were very small but they concluded that smoking may be a risk factor for pulmonary LCH in patients previously diagnosed with LCH [97].

LCH is not hereditary although familial cases have been reported, most frequently in monozygotic twins [129, 130]. Familial cases are further described in section 2.5.2.

Genetic factors may be involved, suggested by familial susceptibility in some cases, and an increased risk of cancer [91]. Although there have been a few genetic studies there have as yet been no genetic analyses of familial cases. Da Costa et al, in a comprehensive multi-national study testing for genomic defects using 72 samples, found no evidence of abnormalities although unidentified genes may still be involved [131].

LCH has been described as a reactive disorder because of the association between pulmonary LCH and smoking. In contrast others have described it as neoplastic. LCH cells have been found to be clonal which may be a feature of cancer or a localised inflammatory response [132-134]. Clonality has been demonstrated in several studies using a Human Androgen Receptor gene Assay (HUMARA) which can distinguish clonal or polyclonal X chromosome inactivation patterns in female tissues [132, 133]. In female LCH patients heterozygous for the HUMAR gene, in a clonal population of cells, inactivation will occur consistently on one chromosome whereas in polyclonal cells some will show inactivation on the paternal X chromosome and some on the maternal X chromosome. The disease is unlike cancers in other respects; the forms are heterogeneous, there is a high probability of survival in most cases and the occurrence of spontaneous regression, even in MS cases [11, 133]. However, abnormally shortened telomere lengths seen in pre-malignant lesions and some cancers, including leukaemia, have been observed in LCH cases with disseminated disease [135].

Although LCH is caused by a proliferation of Langerhans-like cells and other cells of the immune system there is no evidence of it being a primary immune disorder. An over-production of proteins (cytokines) which regulate the immune system has been found in LCH cases [8, 136] as has a decreased capacity of antigen presentation in LCH cells [137]. An abnormal immune response may be triggered by some external factor such as a virus but investigations of viruses in LCH lesions have been inconsistent [133, 138]. In a study published in 1994, McClain et al investigated the presence of common viruses which affect children under five years old, the age group in which the incidence of LCH is the highest. Their case-control study, used bone and lymph biopsy specimens from 56 cases; the controls had reactive hyperplasia, Hodgkin's disease and dermatopathic lymphadenopathy. They tested for nine viruses but found no significant difference in viral infection between LCH cases and controls [138]. Subsequently,

Glotzbecker et al found an association with Human Herpes Virus (HHV) in cases of bone LCH. However, their results were not repeated in a second study the following year using more specialised techniques [139, 140]. It is possible that other common viruses (such as RSV) which were not tested for may be involved or that, at the time of the biopsy, the agent which triggered the disease was no longer present.

There is also little epidemiological evidence of viral illness leading up to the onset of disease. A few associations such as maternal infections and familial thyroid disease have been reported but there is no conclusive evidence of causality. A time-space cluster was reported in a community in Arizona/Mexico by Kramer et al as evidence of a shared environmental exposure [118]. However, numbers were extremely small; there were three cases over a five–year period (section 2.5.4). The cause of LCH may be a combination of genetic, infectious and environmental factors. Associations with LCH and case-control studies performed to assess risk factors for the disease are discussed further below.

2.5 Risk factors and associations

2.5.1 Exploratory studies

In Carstensen and Ornvold's study no association was found with previous disease, delivery route, birth complications, low birth weight or blood group or type [1]. Risk factors for the development of LCH were further investigated in two large cohort studies in the US in the mid-1990s [141, 142]. Patients were ascertained from several institutions around the country plus the Children's Cancer Group. Data were collected by self-completion questionnaires sent to parents which addressed demographic details, pregnancy and birth, childhood diseases, maternal diseases, drug usage, residential and family medical history and environmental factors. The questionnaires had been developed for previous studies of potential risk factors for childhood cancer.

The first of these studies by Hamre et al was a case-control study of 200 individuals aged less than 21 years, diagnosed between 1971-1986 at several institutions. Information was collected from clinical notes and by a 22-page questionnaire completed by parents. 56 cases were lost to follow up or did not return questionnaires. Clinical data were available for 144 cases and questionnaire data were available for 177 cases. Cases

were compared with two control groups, the first being a group diagnosed with various childhood cancers. It was thought that recall by parents of children in the cancer control group and the LCH group would be very similar. However, any risk factors common to both groups might not be obvious and for this reason, a second control group (a community group) was selected. All three groups were matched on age, ethnicity, region and income [142].

The clinical features of disease in the LCH cases were similar to other reports: 62% had SS disease (bone 80% and skin 14%) and 38% had MS disease, 77% of whom were under three years of age at diagnosis. The male to female ratio was similar in all groups (1.4:1 in the LCH and cancer groups and 1.1:1 in the community control group). Family sizes in all groups were also similar. As indicated by the length of the questionnaire, a large number of factors were assessed. LCH was associated with parental exposure to solvents, a family history of benign tumours and infant medication use. However, the factors most significantly associated with LCH were maternal urinary tract infections, and feeding problems and blood transfusions in the child during infancy. In utero transfer of maternal lymphocytes to the foetus may be a possible trigger for LCH. With regard to the other factors, an existing but undiagnosed childhood illness may have led to increased medication, feeding problems or the use of blood transfusions in the neonatal period. The study also found that significantly fewer LCH cases used supplemental vitamins when compared with both control groups. No associations were found between childhood environmental exposures and LCH. The authors carried out multivariate analyses to estimate the strength of these associations and the factors which were independently associated with LCH were family history of benign tumours compared with both control groups, and feeding problems in infancy compared with the control group. The possibility of reporting bias was acknowledged; 24% of cases did not participate and there may have been differential recall between the parents of cases and the community control group. However, they felt that the findings of increased risk with solvent exposure, family history of benign tumours, infant blood transfusions and maternal urinary infections warranted further study.

Following this paper, the same group, led by Bhatia, conducted a second large case-control study to look for risk factors for SS and MS LCH [141]. The same 22-page parental questionnaire was used with another to obtain clinical details from the primary

clinician. 459 children diagnosed aged less than 15 years whose parents were members of the Histiocytosis Association of America and Canada were identified. Patients were categorized into two groups of those with SS or MS disease. As children with SS disease tend to be diagnosed at an older age than those with MS disease it was thought that categorizing them may give some insight into why this occurs. There were 683 community controls and 3719 controls with cancer. LCH patients tended to have been born later, were more likely to live in towns and to have a higher socio-economic status. Adjustments were made for these differences in the analysis, in an attempt to avoid recall and selection bias respectively.

The age and sex distribution in cases was reported to be similar to other studies; the median age at diagnosis was 1.8 years and the sex ratio was 1.1:1. However, the proportion of MS cases (53.8%) was much higher than in their previous study (38%) which may account for the relatively young median age at diagnosis. Postnatal exposures associated with MS LCH included infections (ear, skin, oral thrush) and medication use (mainly antibiotics). Both SS and MS LCH were strongly associated with thyroid disease in the child and in other members of the family although this was reduced after excluding patients with LCH involving thyroid involvement and diabetes insipidus. The lack of vaccinations and chickenpox in childhood were similarly significant risk factors for both SS and MS LCH. There may have been a protective effect from vaccination, although immunisation in these cases may have been delayed because of illness. Gastrointestinal problems were associated with an increased risk of SS LCH as was exposure to solvents (most commonly acetone) although parental exposure was not a risk factor. In this study LCH was not associated with feeding difficulties or infant blood transfusions nor was LCH associated with maternal urinary tract infections as earlier reported by Hamre et al. Although cigarette smoking has been shown to be a risk factor for LCH in adults, a history of smoking in parents pre-conception and during pregnancy was not associated with LCH in children in this study [55, 76].

Although the authors adjusted their analyses to account for the higher socio-economic status of cases, this group of patients, though large, was a ‘convenience’ sample. All parents were members of the Histiocyte Society, 96.5% patients were white and they were more likely to live in an urban environment. Two control groups were used in an

attempt to reduce reporting bias. The association with postnatal infections, lack of immunisations and association with thyroid disease led the authors to speculate that an immune dysregulation may be involved in LCH patients.

No consistent hypothesis regarding risk factors for LCH emerged from these two large studies.

Donadieu et al also studied vaccination in association with LCH [143]. In contrast to the study by Bhatia et al, they found 6/621 cases in which they considered that vaccination may have exceptionally triggered LCH, i.e. that LCH occurred within a month from vaccination and the site of the lesion was in the same area as the injection.

Other studies of pregnancy and birth characteristics have found associations with various malignancies. In a large case control study of 800 individuals in the US, Kaye et al found an association of ALL with birth weights above 3800g in those diagnosed less than four years of age. In addition, history of miscarriage and Caesarean sections suggested an increased risk [144]. In a report from the UK Childhood Cancer Study, Smith et al also found that heavier birth weight is associated with an increased risk of leukaemia; lower birth weight was associated with hepatic tumours [145].

2.5.2 Familial and genetic factors

No clusters or familial cases were found by Carstensen et al in Denmark and none have been reported in other national studies [1]. However, although there is limited data it is estimated that about 1% of cases have a relative with LCH suggesting a genetic component in the development of the disease [129]. Studies have been mainly of twins although as might be expected, if the disease is hereditary, other siblings, parents and cousins with LCH have been reported [122, 146]. In an international study of family clusters, 7/8 monozygotic twin pairs were concordant for LCH compared with 1/10 dizygotic twin pairs and five twin pairs in which zygosity could not be established [129]. In this study there were also two sibling pairs and two sets of first cousins among whom consanguinity was reported. In studies of twins, however, siblings (and to a lesser extent) other family members share a common environment and an inherited disease may only be expressed after a specific environmental exposure.

Arico et al further reported LCH in two generations in four Italian families. The parents were diagnosed in adulthood and 3/4 of their children were diagnosed in childhood. The diagnosis was simultaneous in one family but the time delay between the two diagnoses was between 2-7 years in the others [130]. Given that only a subset of LCH cases is familial, it has been suggested that family members may share a genetic predisposition for the disease although no single gene has been implicated and a common viral aetiology cannot be excluded [130, 147]. Human leukocyte antigen (HLA) typing has been carried out in a few studies. The HLA complex found on chromosome 6 is characteristic for each individual. In a study to examine whether LCH was associated with any HLA antigens, Yu and Chu conducted a study of 74 patients with LCH from Great Ormond Street Hospital and Hammersmith Hospital and compared them with 117 healthy controls [148]. Of those patients tissue typed (46/74) they found an increase in HLA-B7 antigen – 41.3% in LCH patients compared with 16.2% in the control group ($p=0.013$). The authors acknowledged a probable bias in that since patients were recruited from two tertiary centres they were likely to be more severe cases. However, the increase in antigen HLA-B7 was not associated with either SS or MS disease or with disease outcome groups (inactive disease, active disease and death). In a later study of 29 patients and 37 healthy family members, McClain et al examined the frequencies of HLA types and compared them with published frequencies. They found an increase in two antigens (DR4 and Cw7) in Caucasian LCH cases (21/29) which were particularly frequent in those with SS bone disease. (There were insufficient numbers for analysis of cases of other ethnicity.) Unaffected family members also showed an increase in the prevalence of one of these antigens (DR4) compared with published frequencies and controls tested during the same period [149]. They suggested that individuals with these HLA types may have increased susceptibility for specific types of LCH. In addition, a study by De Filippi et al found that patients with SS or MS disease had different genetic characteristics (cytokine genes) which they suggested may vary susceptibility to LCH [126].

2.5.3 Ethnicity and socio-economic factors

Cases of LCH have been reported from many parts of the world and while there has been a predominance of white children in published literature this may be a bias in reporting. Raney et al reported that the incidence of LCH in the Greater Delaware Valley between 1970-1984 was 9% for black children which was lower than the

percentage of blacks in the local population (15%) [113]. In a UK hospital series between 1980-87, 8/58 (13%) cases were 'Asian, oriental or negroid' and in the US, in a study of cases between 1974-1979, 21/92 children were Latin-American, black or American Indian (22%) [90, 150]. The proportions of Caucasian to non-Caucasian children in each of the four groups they studied (based on the progression of disease) were similar.

None of the above was a population-based study. The West Midlands Children's Cancer Registry registered 13 cases of LCH over a five-year period 11 of whom were Caucasian and one was Asian (the ethnicity of the other case was not stated). The proportion of non-Asian and Asian LCH cases in the registry were 2.2% and 2% respectively [33]. In Stockholm County, Stalemark et al reported 29 cases of LCH over a ten-year period of whom eight (27%) were of non-Caucasian European origin. However, it was not stated whether this proportion of non-Caucasian patients was representative of Stockholm County and there is little evidence for an association with ethnicity [28].

Bhatia et al found that their LCH cases belonged to a "higher socioeconomic status, were more likely to live in urban areas and had a higher percentage of white subjects compared with their control groups". However, the authors felt that the difference between cases and controls was probably explained by the fact that the parents of the children included were all members of the Histiocytosis Society and as such, were not representative of the case population [141].

2.5.4 Seasonality and environmental factors

Patterns of disease may vary by geographical location, for example, lung disease appears to be more common in China and orbital disease more common in Mexico [118, 151]. Kramer et al described three cases of orbital LCH in children born in a community in Arizona/Mexico – an incidence of 26 times the expected rate of 1.5 per million ($p=0.0001$) [118]. The study was of three children born over an 18-month period and diagnosed aged between 21-24 months. The cases were all from middle class families which represent approximately 20% of the local population among which additional cases may not have been reported. In spite of the very small sample size, the authors felt that this time-space cluster was evidence of a shared environmental exposure

particularly as increased rates of other diseases (including leukaemia and multiple myeloma) had been reported. Braier et al have reported larger proportions of cases with lung and liver disease in children in Buenos Aires [103, 152]. Between 1987 and 1999, 66 MS patients were identified from a hospital series of 182 and 36 had liver involvement (20%). In a later study they found pulmonary involvement in 36/220 patients (16%), 34 of whom had MS disease. The reasons for these differences are unknown but may reflect environmental or genetic differences in the populations.

A few studies have reported possible seasonal variations in diagnosis or onset of LCH which may be suggestive of an infective aetiology; certain viruses may be more prevalent at particular times of the year. Seasonality can also include some environmental factors that have seasonal variations in exposure levels. Variations in temperature, rainfall and sunlight may influence human behaviour and consequently the spread and load of infection. In a different study in Mexico, by Soto Chavez et al, the onset of LCH was mainly during the rainy season and was more commonly found in patients residing in (colder) high altitude inland cities [153]. In a second report, however, with three more cases, they found the peak month of first presentation of the disease was March (just before the rainy season) with the peak month of birth being September [154]. The reports are from abstracts and there were few data available for these analyses (38 cases with month of onset and 21 with month of birth). However, the authors' suggestion that environmental factors may be important in the onset of LCH may warrant further investigation. In Taiwan, Chen et al studied cases of LCH over a five–year period and found a higher incidence during the summer months in 1997-1998 when rainfall was at its peak during a very severe El Nino [119]. The increased incidence (which did not occur in childhood cancers) was accounted for by a significantly higher number of cases with disseminated disease ($p=0.012$), particularly those with multifocal bone disease ($p=0.017$), compared with other years; these cases were also diagnosed at a younger age. In addition, reactivation and progression was found to occur more frequently in cases presenting during this El Nino. In a study of 29 cases in Stockholm County over a 10 year period 76% of cases were diagnosed during autumn and winter months [28]. Significantly, all nine cases with MS disease and 3/5 with SS disease who went on to develop MS disease were all diagnosed during the autumn or winter. Although LCH is associated with diagnostic delay (which may affect the interpretation of any seasonal variation) the authors reported that the median time

from parental observation of symptoms to diagnosis was only one month. They concluded that infections or other environmental factors may be associated with the development of the disease.

In utero exposure to infections during early pregnancy may cause disease as the foetus is more at risk of damage at that time. However, in their study in the Northwest region of England, Alston et al found no evidence of seasonality by month of birth, month of first symptom or month of diagnosis [2].

The infections specified by Bhatia et al which may increase the risk of LCH were ear infections, bullous impetigo and oral thrush [141]. Several viruses have been studied in connection with LCH including human herpes virus and cytomegalovirus but as discussed in section 2.4 there is no consistent evidence for a viral cause of LCH and further studies are needed [138, 139].

2.5.5 Associations with cancer

LCH has been associated with childhood cancer, including both leukaemias and solid tumours, and is more frequent than could be expected by chance [91, 155, 156]. The Histiocyte Society Malignancy Registry which was established in 1991 identified 73 cases of children less than 18 years old with malignancy. Those most often diagnosed were solid tumours (27), acute myeloid leukaemia (AML) (23), acute lymphoblastic leukaemia (ALL) (16) and lymphomas (7). ALL tended to precede LCH, and solid tumours and AML mainly occurred later, possibly as a result of therapy for LCH. Tumours occurring in the radiation field of treatment for LCH suggested that it was inducing malignancy in these patients and radiotherapy is no longer used [91]. Consequently, in future, fewer cases of AML and solid tumours may be observed. ALL was associated with 16 cases of LCH. It preceded LCH in 10 cases; the median interval between the diagnosis of ALL and subsequent LCH ranged between 0.3-5 years. The authors speculated that LCH may have been induced while the patients were immuno-suppressed while receiving treatment. In the six cases of ALL diagnosed after LCH the interval between the diagnoses ranged from 3.7-7 years [99]. There were seven cases of LCH with either neuroblastoma or retinoblastoma which may indicate a common genetic predisposition [91, 157].

Haupt et al investigated the risk of secondary leukaemia after treatment for LCH with etoposide (now excluded) in two cohorts of over 600 cases (an Austrian-German-Dutch-Swiss cohort and an Italian cohort) [155]. Secondary leukaemias (AML) only occurred in the Italian cohort. Characteristics of both groups were similar although the Italian group had received higher cumulative doses. In the particular subtype of AML reported, aberrations occur on chromosomes 15 and 17 in virtually all cases. An exchange of material between these two chromosomes occurs (reciprocal translocation) resulting in the formation of two hybrid genes (fusion genes). The authors suggested that, since this variant of AML is more common in Italy than in other European countries and is also more frequently reported among other Latino populations and Japanese, "the break points on either chromosome 15 or 17 that are involved in the translocation are more fragile in these populations". The higher doses of etoposide that the Italian group received may have lead to these chromosome mutations.

2.5.6 Congenital anomalies

The frequency of congenital anomalies in patients with LCH was reported by Sheils and Dover in a case control study in Baltimore in 1989 [158]. 39 cases were identified over a 30 year period and were compared with control groups of childhood bone cancer and children with suspected child abuse, matched on sex and race. 18% of the LCH group had a major congenital abnormality compared with 3% and 8% in the other groups. LCH cases with congenital anomalies were more likely to have MS disease involving risk organs and earlier onset of disease; only one case of unifocal disease had congenital anomalies. Since the study included cases diagnosed 30 years earlier, not all were diagnosed histologically and the authors were wary of sampling bias. However, the LCH group were thought to be representative of published LCH populations. They also considered the possibility that patients with congenital defects may require treatment which increased the risk of LCH although no evidence of iatrogenesis had been reported.

In a US study of mortality from Letterer-Siwe disease 1960-1964, Glass et al suggested that LCH may begin before birth given the peak in the frequency of deaths in infants and the deaths of five pairs of siblings, including one pair of twins [122]. They suggested that if congenital anomalies and LCH were concurrent, as in the case of some childhood cancers and congenital anomalies, this might be interpreted as evidence of a

prenatal oncogenic and teratogenic agent. (At that time (1968) no congenital anomalies in LCH cases had been reported.)

2.5.7 In vitro fertilization (IVF)

There have been three publications (based on overlapping data) reporting cases of LCH in children conceived by in vitro fertilization [159-161]. In the second, Kallen et al collected data on over 16,000 children born in Sweden (1982-2001) conceived after various types of IVF and matched them with the Swedish Cancer Registry to assess morbidity and cancer risk [160]. 29 children with cancer or LCH were identified over a 1-20 year follow-up period (median 5.5 years). There was no significant increased risk of childhood cancer. However, the expected number of cases of LCH was 0.9 compared with the observed number of five (RR 5.6, 95% CI: 1.8-13.0). This excluded an additional two cases which were identified from hospital registers which were not reported to the Cancer Registry. This apparent increased risk of LCH in children conceived by IVF was not confirmed in their most recent study with a larger cohort of 26,692 children and only one additional LCH case although there was a moderate increased risk of cancer (OR 1.34) [161].

2.5.8 Associations with other conditions

As well as cancers and congenital defects, LCH has been reported to be concurrent with other conditions. Most of the reports of co-morbidity have been of small numbers of cases or among hospital series. However in a large multi-centre survey in France of 348 cases, 11 children had different concurrent conditions including two cancers [56]. Associations include sclerosing cholangitis, myelodysplasia and other histiocytic conditions – HLH, juvenile xanthogranuloma and Erdheim-Chester disease [103, 162-165]. The authors speculated that overlap in these conditions might be due to a common histogenetic background. Cases have also been reported with partial DiGeorge syndrome and Evans syndrome both of which are disorders of the immune system [166, 167]. In the case of the latter, it was thought that cytokine imbalance in LCH may have played a role in the development of autoimmune disease.

2.6 Mortality and survival

The few national studies of LCH which have reported mortality or survival rates are tabulated in table 2.9. Mortality ranges from 1-12% and survival is around 90% after five years. The majority of deaths were among those with MS disease, particularly with risk organ involvement.

In addition to these studies, Glass et al reported mortality from Letterer-Siwe disease (disseminated LCH) in the US between 1960-64 by age, race and sex in children under 15 years [122]. There were 270 deaths, 157 males and 113 females (ratio 1.4:1); 240 were white and 30 were non-white. There was no significant annual variation between States. Deaths declined with increasing age; the majority (163 (60%)) being under two years of age with only a few deaths aged 3-14 years (57 (20%)). For those under two years of age, deaths from Letterer-Siwe (MS) disease, which is more common in this age group, were estimated at between 3-5 per million per year. However, the study relied on coding of the cause of death from the death certificate (ICD 202.1 – "other neoplasms of lymphatic tissues") and the term "reticuloendotheliosis", and it is possible that other histiocytic disorders may have been included. In particular, the inclusion of five pairs of siblings raises the possibility that deaths were from familial HLH (which has significant mortality) [14].

Recently, Donadieu et al investigated death from LCH in France between 1979-2005 using data from the French LCH Registry and national death certification registry [168]. Deaths were obtained based on appropriate ICD codes for the cause of death and, in addition, the text of the cause of death was checked. For the later years of the LCH registry (2000-2005) data is particularly good for those aged under 15 years old since it was collected prospectively. There were 791 deaths of all ages. For those under 15 years the death rate (per million per year) ranged from 1 in 1980-1990 to 0.5 between 1990-1999 and 0.1 since 1999. This decrease reflected the more aggressive therapy and curability of the disease over the decades. In the whole population, the death rate declined from 0.8 to 0.35 per million per year with the most frequent causes of death in adults being respiratory disease, liver failure and neurological complications.

Various clinical studies with over 50 patients have reported similar survival rates to those in national studies [84]. Willis described survival of 71 patients in California over

25 years with a median follow up of 8.1 years. All except one patient were diagnosed before the age of three years [101]. Survival at 15 years was 83%, 100% and 76% for SS skin disease, bone disease (unifocal and multifocal) and MS disease respectively.

In the UK, Nanduri reported that 36/275 (13%) cases of LCH (all MS) at Great Ormond Street Hospital diagnosed between 1966-1998 died [63]. Leavey et al reported 21% mortality among 41 cases in Dublin over three decades (1959-1989) although survival increased from 57% to 95% with only one death in the last decade [23]. Similarly, in the Northwest of England study of 101 cases, survival increased from 57% in 1954-1968 to 74% in 1985-1998. Improved survival in this region after 1969 was related to different chemotherapy regimen and the employment of a paediatric oncologist [2].

In 1991 the Histiocyte Society introduced the first international clinical trial for the treatment of MS LCH and has since introduced further trials which categorise patients depending on the severity of disease. The results have been compared with previous European multi-centre clinical trials and mortality remains similar at around 20%, the probability of survival being around 80%. It is thought that for patients who do not respond to treatment within the first six weeks the probability of mortality is 75% within two years from treatment. Clinical trials have also reinforced the efficacy of conservative treatment for those patients thought to be less at risk thus reducing possible toxic effects [74, 169].

Table 2.9 Deaths from LCH and survival rates reported by national studies

Author	Year	No of cases	No of deaths	Disease type	Interval between diagnosis and death (median) (months)	Median age at diagnosis of deaths (months)	Survival (years after diagnosis)
Carstensen [1]	1975-1989	90	9 (10%)	9 MS (8 RO+)	Within 6 months		
French Group [56]	1983-1993	348	28 (8%)	26 MS RO+	11.9 (range 0-64)	8.5	90% at 4 years
Kaatsch et al [20]	1980-1992	488					90% at 3 years, 88% at 5 years
Muller et al [27]	1981-2000	111	14 (12%)	14 MS			88.3 at 5 years, 87.3% at 10 and 20 years
Guyot-Goubin et al [3]	2000-2004	212	2 (1%)	2 MS RO+	Within 12 months		99% at 1 and 2 years

2.6.1 Mortality risk factors

As described above, the site of disease, i.e. whether risk organs (liver, spleen, lungs, bone marrow) are involved, is the most important factor in determining mortality especially if there is poor response to initial treatment [74, 92]. Although MS disease is more common in younger children, age is not an independent predictor of a poorer prognosis [169]. With regard to the reporting of mortality and survival, the era in which treatment occurred may also be important because the introduction of more aggressive treatment (combination therapy as opposed to monotherapy) and greater understanding of the progression of the disease has resulted in increased survival [84].

In a review of cases in Dublin between 1959-1989 all deaths were under two years of age and had liver involvement [23]. Similarly liver and spleen involvement was a risk factor in survival of cases in the Northwest of England. Five year survival was only 25% for these cases compared with 78% for those without liver involvement ($p<0.0001$) [2]. In the study of 348 cases in France 26/28 patients who died had organ dysfunction [56].

In addition, although there is a reported predominance of male cases of LCH, boys may be at a higher risk of mortality than girls. In the French study (above), in which the sex ratio was 1.3:1, 82% of deaths were male [56].

2.6.2 Risk factors for permanent consequences

Permanent consequences of LCH were described in section 2.1.6. Risk factors depend on the initial site, extent and recurrence of disease and organ dysfunction. In a study in Stockholm of cases over 39 years, children with MS disease had a poor outcome; only 33% (7/21) had no permanent consequences compared with 58% (14/24) of those with SS skin or uni- or multifocal bone disease [97]. Similarly, a study by the Histiocyte Society Late Effects Group reported that significantly more cases with MS disease had permanent consequences compared with those with SS disease (71% vs 24%, $p<0.0001$). This study, with data from twelve oncology centres, had a disproportionately large number of MS cases (108 compared with 74 SS cases). Cases of SS disease may have been less likely to have developed sequelae and more likely to have been lost to follow up, leading to an over-estimation of permanent consequences

among survivors. Risk factors for various permanent consequences reported in this study are shown in table 2.10 [102].

Grois et al found that those with MS or SS disease of the craniofacial area have a higher risk of developing diabetes inspidus [73]. Similarly, Jubran et al reported that in patients with MS disease the risk of diabetes insipidus was six times higher than in those with unifocal bone disease. Diabetes insipidus was also associated with skull lesions in this study [94].

Table 2.10 Risk factors for permanent consequences of LCH (from Haupt et al) [102]

Permanent consequences	Risk factor
Diabetes insipidus	LCH in skull or ear or central nervous system
Neurological	LCH in ears, facial bones, orbit or diabetes insipidus
Growth retardation	LCH in facial bones or diabetes insipidus
Orthopaedic	Young age at treatment

Reactivation of disease also increases the likelihood of permanent consequences which correlates with the site of disease activity [58, 94, 96]. In a more recent publication from the International LCH Registry of over 335 cases with MS disease (excluding intracranial disease), LCH reactivation was estimated to increase the risk of permanent consequences two fold compared with those without disease recurrence. Reactivation did not, however, increase the risk of mortality; most reactivations were lesions of the skeleton and risk organs were rarely affected [98].

In the Histiocyte Society study by Haupt et al, the effect of age at treatment was assessed; children with skeletal LCH aged under three years at diagnosis had a higher risk of developing permanent consequences than older children when followed up aged 14 years or above [102].

Chapter 3. Methods of ascertainment

Given the rarity of LCH, studies on at least a national level are required to estimate its incidence and to obtain sufficient numbers of cases to fulfill the aims of the study. Since a single source is unlikely to ascertain all cases of LCH, multiple sources were considered to be necessary. Children with LCH may be seen by paediatricians and clinicians of various specialties and therefore this study aimed to approach as many specialists as possible. Four sources of cases were chosen and these are described below. To identify cases and gather information to achieve the study aims (described in Chapter 1) and identify any potential risk factors for the disease, a questionnaire was devised, to be completed by reporting clinicians. The questionnaires used are detailed below as well as the methods of ascertainment and data collection. A summary flowchart of methods used is shown in Appendix C.

Prior to commencing the surveys, an application for Multi-centre Research Ethics Committee (MREC) approval was submitted by the author in April 2003 and approval was obtained from The London MREC in May 2003. Appropriate ethical approval was also obtained for the Republic of Ireland.

Part-funding was obtained from the Histiocytosis Research Trust (HRT), a registered charity founded by a parent group. The main aim of the HRT is to fund research and scientific study into the causes of histiocytosis and the development of improved methods for diagnosis and treatment. They also provide information and support to families affected by histiocytic disorders [170]. A successful application was made for an additional year's funding during the course of the study.

The study commenced in June 2003. Cases were ascertained via the British Paediatric Surveillance Unit (BPSU), a complementary postal survey of other clinicians (carried out from Newcastle), the Children's Cancer and Leukaemia Group (CCLG), and death notifications from the Office for National Statistics (UK) and the Central Statistics Office (RoI). To increase awareness of the study before it started, it was publicised in the BPSU Newsletter. In addition, leaflets, adapted from the study protocol (and produced by another member of the study team), were sent to members of the Royal

College of Paediatrics and Child Health and the Royal College of Radiologists. Surveillance ended in June 2005 and follow up of cases was at one and two years after diagnosis.

As mentioned in section 1.8, it was hoped that the study would eventually contribute to a wider investigation also involving Canada and the Netherlands. To this end, copies of the study protocol were sent to collaborators in both countries. The Canadian Paediatric Surveillance Program (CPSP) began a survey of LCH in 2009 [46].

3.1 British Paediatric Surveillance Unit (BPSU)

The BPSU is part of the Research Division of the Royal College of Paediatrics and Child Health (RCPCH) [39, 171]. It was founded in 1986 in collaboration with the Health Protection Agency and the Institute of Child Health (London). It is currently funded by the Department of Health and is run in partnership with Health Protection Scotland (HPS) and the Faculty of Paediatrics of the Royal College of Physicians of Ireland. Its remit is to facilitate epidemiological research into rare diseases and conditions – usually those expected to have less than 300 cases per year. Studies of incidence alone are not undertaken. It also aims to increase awareness of and disseminate information about uncommon disorders. Since its inception over 60 studies have been carried out, including a study on a related histiocytic disorder, haemophagocytic lymphohistiocytosis (HLH) in 1991.

There is a two-phase application process for studies. An outline is submitted for consideration in the first instance. If approved in principle, more details are requested including the questionnaires and letters which will be used to collect data. The author began participation in the study at this stage. The proportion of cases that might be reported through the BPSU is considered. If this is not high, then sound mechanisms are needed to ascertain cases through other sources. Additional sources of ascertainment are in any case desirable to improve ascertainment [45]. Each application is vetted by the Executive Committee to ensure that studies comply with eligibility criteria and that funding and organisational support will be available. Studies must have relevant ethical, Caldicott Guardian and data protection approval before they can begin and (since 2005) must have National Information Governance Board (NIGB) approval

[172]. This approval is now required to obtain patient data without patient consent and is discussed further in section 3.13. However, in this study NIGB approval was not sought. It is a condition of BPSU studies, that they do not seek patient consent as case ascertainment is more likely to be incomplete and subject to bias, and delay monthly case reporting.

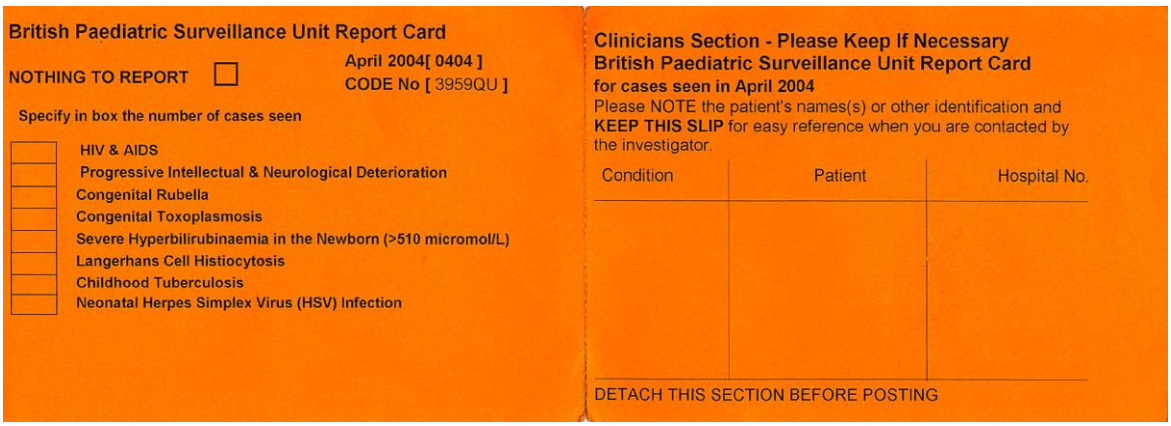
Non-eligible BPSU studies also include clinical trials, case control studies, registry development, and those requiring long-term follow up or retrospective reporting. The system is essentially anonymous since no patient identifiable data passes through the BPSU. There is an annual charge for surveillance and studies are publicised in their quarterly and annual reports.

Surveillance for this study was undertaken for one year from mid-2003 in the first instance. An application was made by the author to continue for another year (2004 to mid-2005) to confirm the number of cases reported in the first year and to give sufficient numbers to look for any patterns in presentation and delays in diagnosis.

3.1.1 Modus operandum

The BPSU operates an active surveillance method. There is a monthly reporting system using a mailing list of over 2300 consultant paediatricians in the UK and Republic of Ireland. The list comprises mainly general paediatricians but also a number of specialists including dermatologists, histopathologists, metabolic disease specialists, endocrinologists, haematologists, oncologists and pathologists.

Figure 3.1 Case report card - "Orange card"



British Paediatric Surveillance Unit Report Card

NOTHING TO REPORT ☐

April 2004[0404]
CODE No [3959QU]

Specify in box the number of cases seen

- HIV & AIDS
- Progressive Intellectual & Neurological Deterioration
- Congenital Rubella
- Congenital Toxoplasmosis
- Severe Hyperbilirubinaemia in the Newborn (>510 micromol/L)
- Langerhans Cell Histiocytosis
- Childhood Tuberculosis
- Neonatal Herpes Simplex Virus (HSV) Infection

Clinicians Section - Please Keep If Necessary
British Paediatric Surveillance Unit Report Card
for cases seen in April 2004
Please NOTE the patient's names(s) or other identification and **KEEP THIS SLIP** for easy reference when you are contacted by the investigator.

Condition	Patient	Hospital No.

DETACH THIS SECTION BEFORE POSTING

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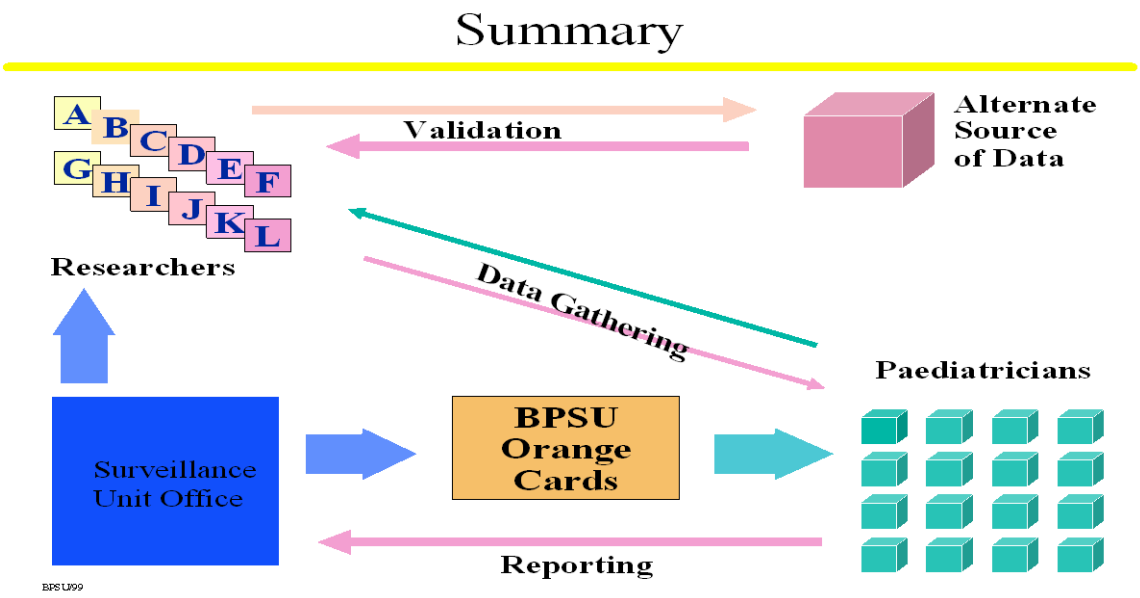
Every month paediatricians receive a two-part case report card ('orange card') with a list of conditions being studied (figure 3.1). They are asked to report any newly diagnosed or suspected cases seen in the past month for whatever reason they have been referred and regardless of whether they are the main clinician responsible for the patient. If they have seen a child with a condition listed, they tick the appropriate box on one half of the card and return it to the BPSU. The clinician keeps details of the patient(s) reported on the remaining half. There is an additional box on the card indicating 'no cases to report' and clinicians are asked to return cards whether or not they have seen cases of interest. The return rate is reported to be over 93% [39]. The names of the reporting clinicians are then forwarded to the investigating team. The reporting system is summarised in figure 3.2.

Figure 3.2 BPSU reporting system



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All paediatricians who reported cases to the study were sent letters asking them to provide further information (including family history, referral and diagnosis details) by completing the study questionnaire and returning it to Newcastle in a prepaid envelope.

Once the questionnaire had been returned by the clinician an audit form was completed for BPSU. This indicated whether a case had been confirmed, was a possible case, a duplicate, had been reported in error or whether follow up had not been possible. A copy of the BPSU response form is shown in Appendix D. Periodically throughout the surveillance period the BPSU sent a list of cases notified and the outcome was recorded on their database for cross-checking.

Annual reports of study progress were produced for 2003-2004 and for 2005-2006 and in addition, quarterly reports and bulletins were produced for the BPSU at regular intervals.

3.2 Newcastle-based survey

A Newcastle-based postal survey was also conducted to include clinicians who were not members of the RCPCH but who may diagnose or see children with LCH. A mailing list was compiled from various sources. Convenors of RCPCH specialty subgroups were approached to ask for a list of their members and for permission to include them in the mailing exercise. In addition, medical directories and hospital web pages were used to obtain a list of specialists (both paediatric and non-paediatric) which included oncologists, endocrinologists, haematologists, gastroenterologists, dermatologists, pathologists, orthopaedic surgeons, rheumatologists, radiologists and respiratory paediatricians. It was thought that histopathologists, in particular, would be key in notifying cases and would complement those reported by paediatricians. A list of sources is given in Appendix E. Since the BPSU mailing list comprises some specialist paediatricians it was made available for cross-checking with the postal survey list to avoid duplication.

Clinicians were mailed four times over a two-year period (November 2003 and 2004, and June 2004 and 2005) inviting them to notify cases seen in the previous six months. A list of over 2200 consultants was compiled initially which was adapted after the first mailing to 1634. Names and departments were removed for the following reasons: those who informed us that they or their institutes did not see children with LCH, those who had moved, retired or died, letters which were returned unopened, multiple members of the same department or institution who recommended a single clinician. Thereafter the list was adjusted slightly for similar reasons at each mailing. The numbers of letters sent at each Newcastle mailing can be found in table 5.1.

On the first mailing an explanatory leaflet with a definition of the disease and reporting instructions was included with the survey letter and reply slip (see Appendix F). The reply slip included a box to report both children and adult cases to aid clarification. On receipt of a paediatric case report, the clinician was sent a copy of the study questionnaire to obtain further information. In the case of a reply from a pathologist, if stated, the treating clinician was sent a questionnaire or the pathologist was contacted for the clinician's details. Prepaid envelopes were included with the letters to encourage replies.

3.3 Children's Cancer and Leukaemia Group (CCLG) formerly the United Kingdom Children's Cancer Study Group (UKCCSG)

Cases were cross-checked regularly with a third source of ascertainment – those registered by the United Kingdom Children's Cancer Study Group (UKCCSG) which merged with the UK Childhood Leukaemia Working Party in 2006 to form the Children's Cancer and Leukaemia Group (CCLG) [173].

At the time of data collection, the main function of the CCLG was to organise and run high quality clinical trials aimed at improving the outcome and quality of life of survivors. This function has changed in recent years and the CCLG no longer runs clinical trials; these are being carried out at Birmingham University Clinical Trials Unit. The CCLG maintains a Tissue Bank and is custodian of nearly 20 years of research data. It is also concerned with patient and family support and improving services, and in education, communication and fundraising. It publishes guides on children's cancer and a regular magazine for families.

There are over 500 multi-disciplinary members of the CCLG working in 22 paediatric oncology centres in hospitals throughout the UK. There are clinical trials for each type of cancer (and LCH) and development of each trial is devolved to 30 individual working groups. The CCLG Histiocytoses Working Group works with the Histiocyte Society in implementing international clinical trials for the treatment of LCH.

All patients with LCH who receive treatment at one of the children's oncology centres in the UK and Ireland should be registered with the CCLG. However, it is estimated that CCLG have details of 90-95% of all UK and Irish childhood cancers and LCH cases and therefore may not have registered all children with LCH. A formal application was made to the CCLG in January 2004 for data and a confidentiality agreement was completed and signed by members of the study team. Subsequently a list of cases registered by CCLG since the start of the study was provided.

Clinicians with eligible cases identified only via the CCLG were sent the same questionnaires to obtain further details as those identified via the BPSU or Newcastle surveys. Cross-checks were made regularly as there was expected to be a lag time between diagnosis and reporting to CCLG. Cases registered slightly later or earlier than

the study period were checked with clinicians to verify the date of diagnosis recorded by CCLG and establish whether they were eligible for the study or not.

3.4 UK Office for National Statistics (ONS) and Central Statistics Office (CSO), Republic of Ireland

To complete the ascertainment of cases, deaths from LCH, which may not have been reported through any of the other methods employed, were sought from the UK and Irish national registry offices.

3.4.1 UK deaths

The National Health Service Central Register (NHS-CR) is part of the General Register Office which was operated by the Office for National Statistics (ONS) at the time of the study [38]. It is now the responsibility of the NHS Information Centre [174]. The NHS-CR contains birth and death details of all those registered with the National Health Service to maintain primary care medical records within the general practitioner network. As well as births and deaths it records name changes and the movement of patients between health authorities, emigration and related events. In addition to its use in administration, NHS-CR data are also used in medical research, particularly as an epidemiological resource. For example, in a Newcastle study assessing whether there was an increased risk of solid tumors among children whose fathers workers at the Sellafield nuclear installation in Cumbria, the births of all those born in Cumbria between 1950 and 1991 were identified by NHS-CR [175]. An individual's record can further be marked for identification ('flagged') for major events including death, cancer and emigration.

A formal application was made to the ONS ethics committee for UK deaths data in August 2006. The causes of deaths are coded on the NHS-CR database using the WHO International Classification of Diseases (ICD) coding systems described in section 1.3. Several versions of the coding system have been used over the years and ONS are currently using versions 9 (1979-1994) and 10 (1995 to the present time) [16, 176]. A list of individuals with LCH who died aged less than 18 years between 1996-2005 was obtained by searching the NHS-CR for relevant ICD codes (ICD-9 and ICD-10) for LCH. Codes for LCH as both the cause of death and the underlying cause of death on

the death certificate were searched. Table 3.1 shows the ICD codes used by ONS to look for these deaths. There were four codes in total - two version 9 codes and two version 10 codes - which cover the various forms of the disease. A description of the four codes is also shown in the table.

Table 3.1 International Classification of Diseases (ICD) codes used to search death certificates [16, 176]

Coding system	Code	Description
ICD-9	202.5	Letterer-Siwe Disease Acute differentiated progressive histiocytosis Acute (progressive) histiocytosis X Acute infantile reticuloendotheliosis Acute reticulosis of infancy
	277.8	Histiocytosis (acute) (chronic) Histiocytosis X (chronic) Eosinophilic granuloma Hand-Schüller-Christian disease Also “other” in “Other and unspecified disorders of metabolism”
ICD-10	D76.0	Langerhans' cell histiocytosis, not elsewhere classified – Eosinophilic granuloma Hand-Schüller-Christian disease Histiocytosis X (chronic)
	C96.0	Letterer-Siwe Disease Non-lipid reticuloendotheliosis and reticuculosis

3.4.2 Republic of Ireland deaths

Deaths in the Republic of Ireland were checked by approaching the Central Statistics Office (CSO) in 2007 for the number of those who had died with LCH on the death certificate over the same 10 year period. The CSO accounts for the vast majority of official statistics in Ireland [37]. It was established in 1949 as a separate Office from the Irish Government in order to ensure its independence on statistical matters. It is widely used by all sectors of society from Government departments and universities to

the media and general public providing statistics which are internationally comparable particularly with EU countries.

An identifiable list of individuals who had died of LCH was not available. The Vital Statistics Section of the CSO provided only the number of deaths by age and sex for 1996-2005 by searching for ICD-9 codes for LCH. The codes used on the death certificates were notified but the actual causes of death were not. As described above, the ICD-9 code used for LCH Letterer-Siwe disease is 202.5 but the other code (277.8) may be used for conditions other than LCH. Therefore further clarification was requested for a very small number of (potential) LCH cases identified from the first search. Consent was obtained from the General Register Office (who hold death certificates) to enable the text on the death certificates to be checked for the exact cause of death. It was thus possible for CSO to confirm whether any of the childhood deaths during the study period were from LCH or another cause, without sending patient identifiable data. The data provided for 1996-2004 were final figures based on the year of occurrence; deaths for 2005 were preliminary figures based on the year of registration.

3.5 Potential cross-checks of data

The NRCT was approached to cross-check our cases with theirs. However, since the NRCT had not received any notifications of LCH for many years, other than from the CCLG, it was considered that this would only provide an extra check on the cases ascertained by the CCLG and would not add any new cases [177].

After the start of the study an orthopaedic surgeon (member of the British Society for Children's Orthopaedic Surgery) responded to the Newcastle survey and reported that a survey was being set up by the European Paediatric Orthopaedic Society, co-ordinated by a UK member and a surgeon in Vienna. Interest was expressed initially in sharing data. However, in spite of several attempts by the author and other members of the study team to discuss collaboration, no reply was received and thus no progress made.

3.6 Case definitions

Notifications were requested for any new or suspected cases whatever the reason for referral and whether or not they were the main clinician responsible for the patient. Cases were defined as children aged less than 18 years and resident in the UK or Republic of Ireland at the time of diagnosis and newly diagnosed with either (a) or (b).

(a) biopsy-proven LCH; lesional cells (LCH cells) must contain Birbeck granules or be CD1a positive or S100 positive with characteristic H&E morphology.
(b) Lytic bone lesion or pituitary/hypothalamic abnormality with the characteristics of LCH but not biopsied because either
    i. clinical features suggest spontaneous resolution
    or
    ii. the risk of the biopsy procedure in view of the location of the lesion (e.g. cervical vertebra, pituitary mass) is too great.

Although unconfirmed cases might be reported the questionnaire captured information on the method of diagnosis thus enabling the eligibility of cases to be established.

3.7 Questionnaires

Clinicians were sent a five-page questionnaire to collect details of the cases reported. Shorter follow up questionnaires to obtain information about the outcome of treatment were sent one year and two years after diagnosis.

3.7.1 Initial questionnaire

The study questionnaire was designed with input from all members of the study group in discussion with the BPSU and was approved by the BPSU Executive Committee. The questionnaire has seven sections which collected data on: patient demographics; family history, pregnancy, delivery and neonatal history; diagnosis; referral history; system(s) involved and diagnostic procedures; status. These are described below. A copy of the questionnaire and letter to clinicians can be found in Appendixes G and H.

Patient demographics (Section A)

With regard to data collection, the BPSU operates on the basis that patient consent is not sought as this would prejudice the completeness of ascertainment and introduce delay. Consequently, because patient consent is not obtained, there is a requirement that only minimal identifying data are collected to preserve patient anonymity as far as possible. The inclusion of hospital number, NHS number, sex and date of birth were agreed with the BPSU, with the addition of the first part of the postcode, to allow identification of duplicate reports. The inclusion of part of the postcode would also allow regional differences in the incidence of cases, if any, to be assessed.

Family history (Section B)

Certain conditions discussed in the review of the literature in Chapter 2, such as maternal history of thyroid disease and family history of LCH, were suggested as risk factors for LCH in two large epidemiological studies (section 2.5.1) [141, 142]. Questions on these were therefore included, as were questions on country of birth and ethnicity to assess whether there were any ethnic differences in the incidence of LCH. Ethnicity was based on nine categories used in the 1991 Census [178]. Also of interest was the possibility of consanguinity (reported in an LCH study described in section 2.5.2) which is more common in some ethnic groups than others. The offspring of consanguineous couples may be at greater risk of certain rare conditions or childhood illnesses. Higher perinatal mortality and congenital malformation rates have been recorded in the UK, particularly in UK-born Pakistani children [179].

Pregnancy, delivery and neonatal history (Section C)

Questions included maternal health during pregnancy since (urinary tract) infection was found to be associated with LCH in a study by Hamre et al [142]. In two large case control studies of LCH questionnaires addressed a large number of factors including pregnancy and birth [141, 142]. Birth weight and gestational age were recorded in this study as these have also been investigated in association with childhood cancer. These associations were described in section 2.5.1.

Diagnosis (Section D)

This section recorded the diagnosis date and the tissue and histological methods used in diagnosing LCH, i.e. staining and the presence of Birbeck granules (as described in section 1.4).

Referral history (Section E)

The referral history of each case from the onset of symptoms to diagnosis was documented including the first presentation, route to diagnosis (via GP, hospital or tertiary centre) and the number of clinicians and specialties involved. Since some forms of the disease may be mistaken for other conditions, they may be associated with significant diagnostic delay. Early diagnosis may lead to treatment of the disease at an earlier stage, thus improving outcome and survival.

System(s) involved and diagnostic procedures (Section F)

Additional information about diagnosis was recorded – the organs involved at diagnosis or at any time – plus the diagnostic procedures used and any positive or negative findings. Radiological diagnoses were also recorded in this section.

Status (Section G)

As discussed in Chapter 2 there have been reports of cancer both preceding and following the diagnosis of LCH and malignant disease (or history of maligancy) was therefore noted. Such cases are registered by the Histiocyte Society Late Effects sub-group. The date of the last follow up and vital status were included in this section, and whether or not the patient was registered with the CCLG.

Space was also provided at the end of the questionnaire to collect any other relevant information since LCH has also been associated with congenital anomalies and to be concurrent with other conditions such as sclerosing cholangitis and HLH [103, 158, 162].

The questionnaire was piloted by Dr Windebank and colleagues at Newcastle and after some cosmetic modifications to the layout the final version was agreed.

3.7.2 Other potential questions

In the course of developing the questionnaire, the inclusion of other questions was raised. These included a section on environmental exposures – smoking in the household, foreign travel, childhood infections and immunisations, siblings and birth order. Environmental exposures had been investigated in two large case-control studies in the US and there is evidence that first born children are at an increased risk of leukaemia and lymphoma (suggesting an infective aetiology) [141, 142, 180]. However, although of interest, questions on these were rejected by the BPSU for reasons of them being considered better suited to a case-control study.

3.8 Collection of questionnaires

Questionnaire returns were monitored regularly and every effort was made to collect them. Reminders were sent as appropriate to non-responding clinicians at regular intervals by post, email and by phone. In addition, an oncologist (member of the study team) assisted in questionnaire completion for cases at Great Ormond Street Hospital, and other team members were asked to exercise their influence in persuading clinicians to return the questionnaires.

3.9 Case identification

Cases were identified based on questionnaire demographic data, i.e, a combination of sex, date of birth, hospital number, first part of postcode plus date of diagnosis. Those aged over 18 years, diagnosed outside the study period or with a diagnosis of a condition other than LCH were excluded.

3.10 Questionnaire data

3.10.1 Database

A 4D relational database was set up on a Macintosh computer network to facilitate the mailing process and to hold the data. The database and mailing procedures were designed by the Computer Officer in the Institute of Health & Society (Child Health), Mr Richard Hardy, in consultation with the author. An automated process was used for the six-monthly survey of clinicians to produce covering letters and response slips. Clerical assistance was obtained to help with mailing and to record the replies on

database. Dates of initial mailing, receipt of questionnaires and mailing of reminders were recorded.

The database consists of a series of related tables linked by common unique identifiers. As the initial questionnaires arrived data were entered into the Questionnaire table. For each unique patient identified, a single record was created in the Patient table with their demographic data, vital status and diagnosis. Each patient was linked to single or multiple entries in the Questionnaire or Follow up Questionnaire tables by their unique identifier. Similarly, reporting clinicians (in the Consultants table) were linked to single records in the Notification Request table (which recorded their responses to mailing) or to single or multiple records in the Questionnaire tables, depending on whether they reported more than one patient. A figure showing the structure of the database is given in Appendix I.

3.10.2 Data

For analysis purposes datasets were constructed with one record for each LCH case by joining data from the Patient to the Questionnaire or Follow up questionnaire tables. In some cases there were multiple questionnaires for an individual, and data from each of these questionnaires were combined into one record by hand. The combining of textual data, for example, symptoms, referral patterns and comments was especially time-consuming.

Responses from the treating consultant oncologist were regarded as definitive. Inconsistencies which could not be resolved (e.g. dates, type of treatment) were referred to the clinician or their data manager, where possible, or to Dr Windebank. The date of diagnosis was taken to be the date of biopsy, X-ray or autopsy. Where only the month was given for a date, e.g. the date of first symptom, the first day of the month was used.

3.10.3 Data checking

A two-page form was designed by the author to enable all questionnaire data entered on the database to be printed and cross-checked with original paper copies. Additional programs were written in 4D's programming language, for example, to cross-check notifications with the BPSU or CCLG, and to check the validity of the data. Since each

questionnaire was flagged with an appropriate status code, a list of those not returned could be easily produced.

3.11 One-year follow up questionnaire

A two-page questionnaire was sent to the reporting clinician one year after diagnosis (see Appendix J). The sections of the questionnaire were as follows:

A Pre-printed demographic patient information (from the database) to enable the clinician to identify the patient.

B Current vital status and whether the patient was with or without active disease and, if disease was active, whether on treatment.

C The type of treatment received, i.e. whether the patient was 'wait and see', had had curettage, a biopsy or surgery, or was on LCH protocol or other treatment.

D Sequelae/permanent consequences. This section listed ten permanent consequences most often reported in LCH cases as discussed in Chapter 2 (section 2.1.6).

In addition, space was allowed for any other relevant information to be noted by the clinician.

Data were entered in a 'Follow up Questionnaire' table on the database and checked as for the initial questionnaire data. There were fewer cases with multiple Follow up questionnaires as follow up tended to be by only one clinician.

At the end of the one year follow up period in 2006, a representative at each CCLG treatment centre who had reported cases was sent a summary list of patients to check and to return missing information, if appropriate.

3.12 Two year follow up questionnaire

In order to obtain better information on treatment, survival and outcome, MREC approval was obtained by the author in July 2007 for an amendment to the study protocol to send further follow up questionnaires to reporting clinicians. The questionnaire contained the same questions as in the first follow up questionnaire but the design was modified to a single page format. It was hoped that this slightly simplified, shorter format would appear less time-consuming than the previous questionnaires and elicit a speedy response from clinicians [181]. A copy of the two year questionnaire is given in Appendix K. All those who returned a one year follow up questionnaire were sent a second follow up questionnaire.

3.13 Ethics

The main point of ethical concern is that patient consent was not sought to collect patient identifiable data for the study. The BPSU only accepts studies on the basis that patient consent will not be sought on the grounds that ascertainment is likely to be incomplete and subject to bias, and that delay would be introduced.

When ethical approval was sought for this study in 2003, BPSU studies were not required to obtain approval from the National Information Governance Board for Health and Social Care (NIGB) before proceeding. NIGB is a statutory body which can allow patient identifiable information to be collected without the consent of patients under section 251 of the NHS Act 2006 under specific circumstances [172]. This function was formerly carried out by the Patient Information Advisory Group (PIAG). Members of the Board are either members of the public appointed by the Appointments Commission or represent stakeholders in health and social care.

Permission to collect identifiable data without seeking patient consent may be granted by the NIGB Ethics and Confidentiality Committee under the following conditions:

1. the data are only to be used to support medical purposes that are in the interests of patients or the wider public
2. gaining patient consent is not a practicable alternative and
3. anonymised information are insufficient

In this study although neither patient consent nor NIGB approval were sought the first two criteria were met. 1) The data were collected to provide information to inform all those concerned with children with LCH from specialists to parents. 2) Only a relatively small number of cases were likely to be identified but gaining consent from patients was not practicable or compatible with BPSU surveillance methods for the reasons described above. With regard to the third condition, some identifying data were required to identify duplicate cases; a degree of anonymity was preserved as patient names and addresses are unknown.

Patient confidentiality was respected according to the conditions of each of the bodies concerned in this study – BPSU, CCLG and ONS – and, additionally, according to the terms of employment at Newcastle University and those specified by Newcastle Hospitals NHS Trust in Honorary Research Contracts.

At the time ethical approval was obtained, the London MREC indicated that the continuation of BPSU studies without patient consent and without PIAG (NIGB) consent was not sustainable and that sooner or later the issue would have to be raised and resolved. In the intervening years it has become mandatory for new BPSU studies to obtain both ethical and NIGB approval. These are now part of the Integrated Research Application System (IRAS) which is a single system for obtaining relevant research governance approvals for health research in the UK [182].

Chapter 4. Data analysis methods

This chapter describes the statistical and epidemiological methods of analysis used in the study. All statistical analyses were performed using the statistical software packages, Stata version 10 and SAS 913, an epidemiological software package, Epidat version 3.1 and Excel [183-185]; the geographical information system ArcGIS 9.2 was used for mapping [186].

4.1 Estimates of completeness of ascertainment

4.1.1 Capture-recapture analysis (C-RA)

Capture-recapture analysis (C-RA) was used to estimate the number of cases missed by all reporting sources [187]. C-RA was first used in ecological studies to estimate populations of animals by capturing (tagging) and releasing animals and then repeating the procedure (recapturing) them. The number of animals identified by both samples and the number identified by one sample are used to estimate the number not ascertained by either. The method has since been used by human disease registries to estimate completeness of ascertainment and has been applied to epidemiological studies to adjust estimates of incidence or prevalence of a disease by allowing for under-ascertainment of cases [188-191]. It has also been extended to include more than two sources [187].

The underlying assumptions of these methods are:

1) The study population is closed, i.e. there is no change to the study population during the period of data collection.
2) All cases identified by one source can be matched to another source using the same identifiers.
3) The chance of being identified by one source is the same as the chance of being identified by a second source.
4) Capture by one source, is not dependent on capture by another source, i.e. survey lists are independent.

The main criticism of C-RA has been that the assumptions above can rarely be complied with, in particular, 3 and 4. One source may have a greater possibility of identifying cases than another. In addition, the presence of a case from one list may be contingent on being present on another list. For example, LCH cases recorded by NRCT may all have come from CCLG registrations.

Where only two sources are used, the degree of overlap in identification may result in under- or overestimation of the number of cases. Estimates should therefore be viewed with caution. In addition, although C-RA methods may be potentially useful, for example, in estimating disease rates without the use of costly surveys, the requirement for the services of an experienced statistician to apply multi-source modelling methods may be costly [190, 191]. The simplest method of C-R estimation using two sources can be calculated by hand. However, as indicated above, calculations are more complicated with increasing number of sources and additional methods which take account of any dependencies which might exist between sources.

Epidemiological studies and registers, in spite of exhaustive efforts, are likely to miss cases and C-RA gives a method of quantifying undercounting [187, 190]. Bearing in mind the cautions above, an estimate of the completeness of ascertainment was obtained using the two-source model and compared with the results of three-source model analysis which also indicates the dependency between sources.

4.1.2 Sources and models

With reference to the assumptions made when using CR-A (in section 4.1.1), the first two criteria were met – the cases were all newly identified from the same population over the same time period; case eligibility was clearly defined and the same criteria were used to identify individuals. The mailing lists for the Newcastle and BPSU surveys were cross-checked and no clinician appeared on both lists. The chance of being identified by either source was thought to be equivalent since one group of clinicians tended to be involved in the diagnosis of cases (Newcastle survey) and the other in the treatment of them (BPSU survey).

The surveys were thus assumed to be independent sources and were used in the two-source model below (section 4.1.3). The CCLG may not have been an entirely

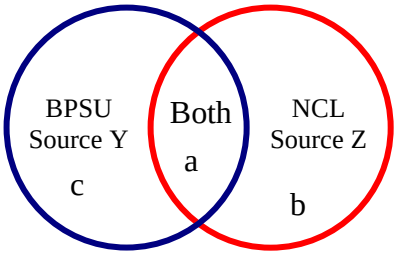
independent source as cases may have been notified by clinicians on either the BPSU or Newcastle mailing lists. The independency of the CCLG, and interactions between all the sources were estimated using three-source model analysis (section 4.1.4). The methods were described by Hook and Regal in 1995 with errata published in 1998 and have been used frequently in epidemiological studies [187, 192].

Both estimates were cross-checked using the Epidat epidemiological analysis package. This is a free distribution program developed by public institutions under the Pan-American Health Organisation (PAHO) which serves as the regional office for the Americas of the World Health Organisastion [185, 193].

4.1.3 Two-source model

This model was used to estimate the completeness of ascertainment by the BPSU and Newcastle surveys and the overall number of cases using the number of cases ascertained by each source and the number ascertained by both (figure 4.1).

Figure 4.1 Cases used in two-source model



The calculations, which were done by hand, are shown in table 4.1. The terms a, b, c denote the numbers observed in each cell and x is the number in the unobserved cell, denoting the number missed. An adjustment of the estimate (the maximum likelihood estimator - MLE) to account for sample bias results in a “nearly unbiased estimator” - NUE.

Table 4.1 Two-source model (from Hook and Regal) [187]

		Source Y (BPSU)		
		Yes	No	
Source Z (NCL)	Yes	a	b	Total $a+b=Z_0$
	No	c	x	
		Total $a+c=Y_0$		

x= unidentified cases

N= a+b+c+x the total number of cases in the population

Estimated values		Maximum likelihood Estimator (MLE)	Nearly unbiased estimator (NUE)
Unobserved cell	x	bc/a	bc/(a+1)
Completeness of source Y	Y_c	$a/(a+b) = a/Z_0$	$(a+1)/(a+b) = (a+1)/Z_0$
Completeness of source Z	Z_c	$a/(a+c) = a/Y_0$	$(a+1)/(a+c) = (a+1)/Y_0$
Total population	$\hat{N}$	a+b+c + (bc/a) or (a+b)(a+c)/a or Y_0/Y_c or Z_0/Z_c	a+b+c + (bc/(a+1)) or [(b+1)(c+1)/(a+1)]-1

Confidence intervals for the adjusted estimate of the total number of cases were calculated by hand as described by Rahi and Dezateux [188]. The variance was calculated by

$$\mathrm{Var}(\hat{N}) = \frac{(a+b+1)(a+c+1)(b)(c)}{(a+1)^2\,(a+2)}$$

and 95% confidence intervals were $\hat{N} \pm 1.96\,(\sqrt{\mathrm{Var}(\hat{N})})$.

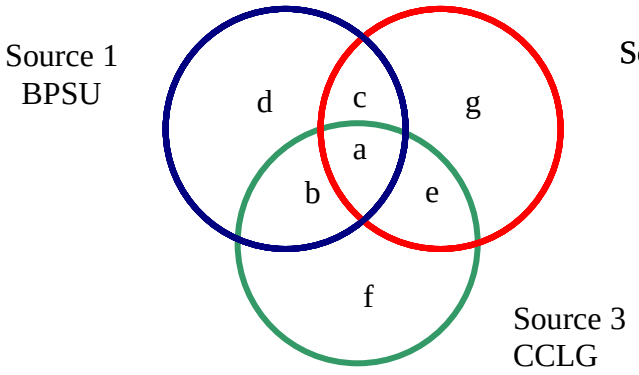
The level of ascertainment was the proportion of total cases expected that were actually identified, expressed as a percentage.

The results of the two-source model are subject to error if the assumptions listed in section 4.1.1 are not met. A large overlap (positive dependency) in cases will result in an underestimation of the population while very little overlap (negative dependency) will result in an overestimation of cases. In spite of the lists of clinicians on the Newcastle and BPSU survey lists being independent a degree of overlap in cases may be expected. For example, a case identified by a pathologist may have been reported via the Newcastle survey and the same case may have been reported to the BPSU by the treating clinician. However, if these clinicians collude and only one of them reports a case the overlap may be reduced resulting in an overestimation of cases.

4.1.4 Three-source model

Multiple-model C-RA allows greater accuracy of estimates of completeness of ascertainment and reduces the problems of source dependence or independence. Since the CCLG contributed cases, but may not have been an entirely independent source of ascertainment (as some reporting clinicians may have also reported cases via one of the BPSU or Newcastle surveys) the estimate of the number of missing cases was performed using three-source (log-linear) modelling [187]. The degree of inter-dependence between the sources was also estimated using this method. Figures 4.2 and 4.3, adapted from Hook and Regal, show the data layout and methods for deriving estimates. The terms a, b, c etc are used to denote both the names of cells and numbers observed in each.

Figure 4.2 Cases used in three-source model



With three sources there are eight possible models. A case can be identified by all three sources, by two out of three, one out of three or none of them. By knowing the frequencies for seven out of the eight possible combinations the number of cases captured by none of the sources can be estimated. The eight different models allow for interaction between the three sources and are compared in the analysis. The simplest is the independent model. Three of the models allow an interaction between two of the sources and further more complicated models allow for two pair interactions.

The estimate of the missing number of cases by each ($\hat{x}$) can be summarised as follows

$$\hat{x} = \frac{\text{(values exclusive to interaction) x (values exclusive to non-interaction)}}{\text{values shared}}$$

An error was spotted in the original paper by Hook and Regal in the estimates of the number of missing cases in the three-source model. This was confirmed by a colleague who found an erratum publication (corrections are shown in bold in figure 4.3) and a more detailed description by Orton et al of how to accomplish the analysis using the statistical package SAS [192, 194].

Figure 4.3 Three-source model (from Hook and Regal including published errata) [187, 192]

		Source 1 (BPSU)			
		Yes		No	
		Source 2 (NCL)		Source 2 (NCL)	
		Yes	No	Yes	No
Source 3 (CCLG)	Yes	a	b	e	f
	No	c	d	g	x

N_{obs} = a+b+c+d+e+f+g

N_1 = a+b+c+d (BPSU)

N_2= a+c+e+g (NCL)

N_3= a+b+e+f (CCLG)

Maximum likelihood estimates of x using alternative models

Model	df*		Model	Estimator†
1	3		Independent	$\hat{x} = \hat{N} - N_{obs}$ ††
2	2	*Equivalent*	1-2 interactions	$\hat{x}$ = (c+d+g)(f)/(a+b+e)
3	2	*to two*	1-3 interactions	$\hat{x}$ = (**b**+d+f)(g)/(a+c+e)
4	2	*independent sources*	2-3 interactions	$\hat{x}$ = (e+f+g)(d)/(a+b+c)
5	1	*Two*	1-2, 1-3 interactions	$\hat{x}$ = gf/e
6	1	*independent*	1-2, 2-3 interactions	$\hat{x}$ = **df/b**
7	1	*subsets*	1-3, 2-3 interactions	$\hat{x}$ = **gd/c**
8	0		1-2, 1-3, 2-3 interactions	$\hat{x}$ = (adfg)/(bce)

*df = degrees of freedom; the unobserved cell = $\hat{x}$;

†Where not given explicitly the total population $\hat{N} = \hat{x} + N_{obs}$

†† $\hat{N}$ is the solution of $(\hat{N} - N_1)(\hat{N} - N_2)(\hat{N} - N_3) = \hat{N}^2(\hat{N} - \mathbf{N_{obs}})$

Rough calculations were made for models 2-8 by hand using the formulae above. Estimates of missing cases and total population, along with corresponding goodness of fit values and confidence intervals for all models were obtained using SAS.

The SAS code published by Orton et al adapted for three sources of data is shown in table 4.2.

Table 4.2 SAS code (adapted from Orton et al) [194]

Source 1 (BPSU)	Source 2 (NCL)	Source 3 (CCLG)	
1	1	1	a
1	1	0	c
1	0	1	b
1	0	0	d
0	1	1	e
0	1	0	g
0	0	1	f

The values of a, b, c etc are the number of cases found by each source or combination of sources. The SAS procedure *genmod* was then run repeatedly with each model as a parameter, e.g. 1-3 (BPSU-CCLG independent of NCL) or 1-2, 2-3 (two independent subsets BPSU-NCL and NCL-CCLG) etc [184].

The best model can be selected by comparing the goodness of fit and the degrees of freedom of each model; ideally the goodness of fit value should be as small as possible with a high degree of freedom. A measure of the goodness of fit of a particular model is the value of the likelihood ratio statistic G^2. In addition, the values of "information criteria", Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC), which can be calculated using the G^2 statistic are used to select the optimal model. Those with negative values are preferred. The model chosen by investigators is usually the least complex with the most adequate fit [187].

The AIC and BIC values were calculated using Excel using the formulae described in Hook and Regal's paper.

$$AIC = G^2 - 2(df)$$

$$BIC = G^2 - [\log(N/2\pi)]\ [df]$$

Where G^2 is the value of the goodness of fit statistic, N the value of the observed population and df the degrees of freedom for each model.

The degree of dependency between the sources was also assessed (table 4.3). There are three different possible two-source estimates that can be obtained by disregarding one of the other sources. An underestimation by a model will suggest positive dependency (a large overlap in cases) while an overestimate will suggest negative dependency (a small overlap in cases).

Table 4.3 Estimate of dependency between sources (from Hook and Regal) [187]

Sources	Two-source restricted estimates of same population *(restricted by disregarding a third source)* $\hat{N}_{MLE}$	$\hat{N}_{NUE}$
1 versus 2	$(N_1)(N_2)/(a+c)$	$(N_1)(N_2)/(a+c+1)$
1 versus 3	$(N_1)(N_3)/(a+b)$	$(N_1)(N_3)/(a+b+1)$
2 versus 3	$(N_2)(N_3)/(a+e)$	$(N_2)(N_3)/(a+e+1)$

MLE maximum likelihood estimator; NUE nearly unbiased estimator

$\hat{N} = \hat{x} + N_{obs}$

The results of the three-way analysis were cross-checked using Epidat [185].

4.2 Population and incidence rates

Incidence and prevalence are commonly used indicators for measuring diseases among populations. Prevalence is a measure of existing cases of a condition in a population at a given time, while incidence is the number of new occurrences of a condition in a population over a given period. Incidence was the measure used in this study and can be defined as follows:

$$\text{Incidence Rate} = \frac{\text{number of newly diagnosed cases over a specific time period}}{\text{population at risk during the same time period}}$$

ONS annual mid-year population estimates for the study period were used (pro rata as necessary) for the UK population [195]. Averages of the 2002 and 2006 Census data were used in calculating the population for the RoI [196]. Age-standardized (to European Standard Population) and age-specific incidence rates were calculated with corresponding 95% confidence intervals. The rate is expressed per million persons per year. For UK regional rates, ONS Government Office Region (GOR) mid-year population data were used pro rata.

4.2.1 Age-standardized incidence rates

Age standardized incidence rates (ASR) of LCH were calculated for comparison with other European studies. Standardisation removes effects due to differences in population structure allowing populations with different age distributions to be compared directly with each other [197]. The ASR is the number of events that would occur in a given country if the standard population lived there and the age-specific incidence rates of that country were applied. The European Standard Population (ESP) which has defined age-groups was used for standardisation. The age specific rates of LCH multiplied by the ESP in the corresponding age groups gave the number of cases of LCH which would be expected in the ESP, if it experienced the UK and RoI age-specific rates.

The following table was used in the calculation and shows the ESP [198].

Table 4.4 The European Standard PopulationTable [198]

Age group	European Standard Population
0	**1,600**
1-4	**6,400**
5-9	**7,000**
10-14	**7,000**
15-19	7,000
20-24	7,000
25-29	7,000
30-34	7,000
35-39	7,000
40-44	7,000
45-49	7,000
50-54	7,000
55-59	6,000
60-64	5,000
65-69	4,000
70-74	3,000
75-79	2,000
80-84	1,000
85+	1,000
Total	100,000

Source: 1991 World Health Annual of Statistics - based on Waterhouse *et al* (eds). *Cancer Incidence in Five Continents*, Lyon, IARC, 1976 (Vol. 3, p 456).

Age standardized rates for all 0-14 year olds and for boys and girls were calculated using the direct method as shown in Table 4.5 [197]. The numbers in each age group of the standard population are multiplied by the incidence observed over the two year period. This number is then divided by the total number in the standard population to give the expected cases in the standard population.

Table 4.5 Calculating the ASR for 0-14 year olds [197]

Age range (years)	No. of children in population	No. of LCH cases	Observed incidence N_x	No. of persons in standard population	Expected cases in standard population	Variance
x	P_x	N_x	R_x / P_x	W_x	$E_x=R_xW_x$	$V_x=E_xW_x/(YP_x)$*
0						
1-4						
5-9						
10-14						
Total						

* Y = number of years on which rates were based. In this study Y=1 as the population P_x is the total population over the study period

The ASR is the sum of the expected cases divided by the sum of number of cases in the standard population, expressed as cases per million per year:

$$ASR = \sum E_x / \sum W_x$$

The method of calculating the standard error is also shown in Table 4.5. The variance was calculated for each age group and the standard error (SE) calculated by summing the variances, taking the square root and dividing by the total number of persons in the standard population.

$$SE = (\sqrt{\sum V_x}) / \sum W_x$$

The 95% confidence intervals were calculated as ASR + or – 1.96 x SE of the rate in the population.

4.2.2 Regional incidence rates

The population studied covers 13 geographic regions. Incidence rates and corresponding confidence intervals were calculated using Stata for each region and the different rates compared. Comparable regional population data for 0-14 year olds were unavailable for the three years over which the surveillance was carried out. Therefore mid-2004 population data for the UK Government Office Regions (GORs) were used to calculate the ASRs for cases aged 0-14 years [199, 200]. For age-specific incidence

rates, different quintiles of population data (for those aged 0-15 years) were available for each of the study years and were used pro rata [195]. 2002 and 2006 Census population data for the RoI were used in calculating both incidence rates [196].

An analysis of heterogeneity was carried out using the Stata command *metan* to determine whether there were genuine differences underlying the regional incidence rates (heterogeneity) or whether the variation in the proportions in each region was compatible with chance alone (homogeneity). This command provides methods for meta-analysis, a process in which data from a comparable set of studies is synthesised to increase statistical power and to investigate discrepancies and inconsistencies between their results. Studies included in a meta-analysis must fulfill predetermined criteria. All must have used essentially the same or closely comparable methods and procedures; the populations studied must be comparable; and the data must include all eligible studies. The command is also suitable for analysis of estimates with confidence intervals or standard errors [201].

The test assumes that there is no significant difference (homogeneity) between the rates. *Metan* uses middle (incidence rate), lower and upper confidence interval values as parameters and generates a graph (forest plot) showing the ranges of these values for each region. Consistency of rates is assessed by using an appropriate weighted sum of the differences between each rate and the overall estimate. The weight that each region contributes is shown by the size of the plotting symbol on the graph. The test generates an I-squared value and a p value; I-squared is the variation in rate attributable to heterogeneity expressed as a percentage; a low p value would indicate that there is a statistically significant difference in the proportions in each region.

4.2.3 Mapping of regional rates and cases

Geographic Information Systems (GIS) are now frequently used by health authorities, emergency services, public health specialists and researchers to identify potential causes of ill health and to assist in health care planning. The focus for health-related uses of GIS is usually on either epidemiology of specific diseases or management of health care services. GIS applications in health studies range from simple mapping and visual display to investigating data relationships, exploring risk factors and modelling the spread of infectious diseases [202-204]. For example, Hjalmars et al used GIS in cluster

detection of childhood leukaemias in Sweden and Dummer et al mapped stillbirth rates in Cumbria comparing wards and postcode districts over four decades [175, 203]. However, mapping problems have been described by Dummer, one being the modifiable areal unit problem (MAUP). Depending on the geographical unit selected large rural areas (with low populations) may have high disease rates which may have only one or two cases and no biological significance [202]. Caution was also advised in mapping p values (to identify areas with extremely high or low observed number of events). Since significance is related to sample size, highly populated urban areas are more likely to have significant p values which are not the result of underlying variation in risk. In practical terms, GIS generates a substantial amount of data although with increasing advances in microtechnology this is becoming less of a problem [204].

GIS choropleth maps, which use shading proportionally to display statistical variables, were used to visualise the differences in regional rates. Incidence rates were calculated for each region, grouped into categories and displayed using gradient shades. The approximate location of cases was also dispalyed.

UK mapping

National and regional digitised boundary (polygon) data for the UK were downloaded from the Edina UKBORDERS service using ArcMap version 9.2. (Edina is a national centre for geographic data for higher education) [205]. The geographic areas were Scotland, Wales and Northern Ireland plus nine English Government Office Regions (GORs). GORs have been the primary classification for the representation of regional statistics since 1996 (figure 4.4) [199]. Six-figure grid references (i.e. Easting and Northing co-ordinates) for cases were obtained from the first part of the postcode data using Edina [205].

The full postcode represents an average of 17 properties ranging from a single code for a large business address to approximately 100 households. However, the full postcode was not available in this study because of the patient anonymity issues discussed in the previous chapter. Either the postcode district or postcode sector, collected from questionnaires, was used. Both postal districts and sectors vary in geographic size depending on the number of households therein. There are approximately 3000 UK postcode districts, e.g. PO1 and approximately 11,500 postcode sectors, e.g. PO1 3 [206]. The exact locations of cases are therefore approximate. The partial postcode

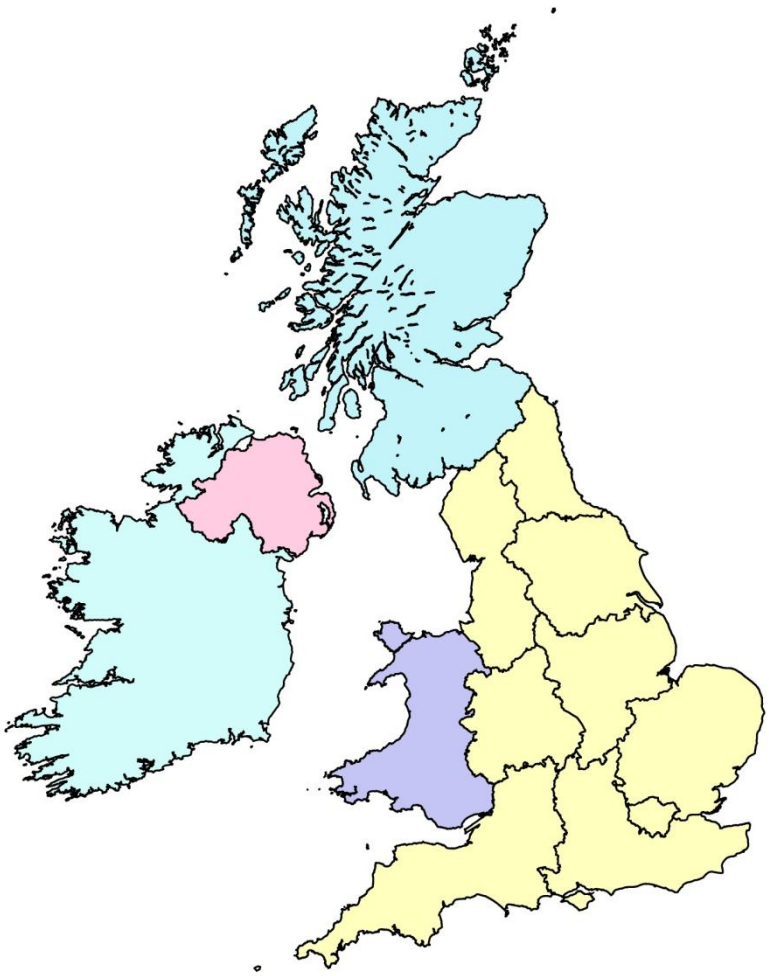
data were however, sufficient to assign each case to a region to calculate regional incidence rates. Northern Ireland postcodes were mapped using the same grid as that used for the RoI, i.e. the Irish National Grid, as opposed to the Great Britain Ordnance Survey Grid.

Republic of Ireland mapping

The Edina service, being a provider of UK data, did not supply a digital boundary map for the RoI. This was obtained from another source, the Digital Chart of the World (DCW), a product of the Environmental Systems Research Institute, Inc. (ESRI). Boundaries and other geographic information of different countries can be downloaded in Arc/INFO export format from their web-site [207]. However, these data (View files) differ in format from Edina data but are compatible with an earlier version of GIS software. Data were converted to a suitable format for ArcMap by importing it using ArcCatalog ArcView 8 conversion tools. The file produced was suitable for adding as a 'layer' to the UK map.

The geographic coordinate systems for UK and DCW maps are different, i.e. British National Grid system (Ordnance Survey GB) versus GCS_Clarke_1866. To avoid alignment or accuracy problems with the data, ArcMap adjusted (transformed) the coordinates automatically to the Ordnance Survey coordinates. The resulting map with English regional boundaries is shown in figure 4.4.

Figure 4.4 Map of the geographical boundaries used to compare regional incidence rates



Postcodes were introduced in the RoI after the end of the study period. Since the RoI was treated as one region all cases reported by clinicians in Ireland were mapped to Dublin and the incidence rate calculated accordingly. Irish and Northern Ireland coordinates use the Irish National Grid system and were mapped using Irish Transverse Mercator Grid [208].

4.3 Epidemiological analyses

4.3.1 Comparisons

The data for all descriptive analyses were provided by questionnaires which varied in their completeness. In a few cases data were provided by data managers in a spreadsheet format. Dates, such as date of diagnosis or follow up, varied in their accuracy; in some cases only the month and year were provided and in these cases the day was taken to be the 1st of the month.

The Mann-Whitney test (Stata command *ranksum*) was used to compare differences between two groups, for example, in the time from symptoms to diagnosis between sexes. The test does not assume a normal distribution. It uses ranking to compare whether observations in one group tend to be larger than in the other (i.e. it compares medians) and calculates the probability of there being no difference between them.

The Kruskall-Wallis test similarly uses ranking to compare more than two groups, for example, differences between types of disease. The test does not assume a normal distribution and is suitable for small samples. The Stata command was *kwallis*.

The Fisher-exact test was used to compare sub-groups of cases, for example, of those with and without active disease, and is suitable for small samples. The Stata command was *tabi*.

The subgroups used were as for survival analyses described below in section 4.4 (table 4.10).

4.3.2 Seasonality

Seasonal variation in birth, symptom onset and diagnosis of LCH may be indicative of an infectious aetiology or the involvement of a seasonal variation in an environmental factor such as sunlight, diet or use of pesticides. An association with month of presentation was reported by Soto-Chavez et al (in section 2.5.4) and there have been contradictory reports of seasonality in association with leukaemia [154, 209, 210]. Potential seasonality was thus assessed using Edwards' test [211]. This test has been used in other epidemiological studies to test for seasonality of events where population data are not available [210, 212]. The model tests whether the distribution of events

follows a harmonic curve (having one peak and one trough) in a single year. The data consist of the frequencies of events (in this study births, diagnoses, first symptoms) grouped into time intervals (months). The data are presented in the form of the circumference of a circle divided into 12 sectors (months). The angle of the maximum rate indicates the peak month. The relative strength of the peak is given by the amplitude – the percentage by which the rate at the peak month is greater than the mean rate for all months combined. However, the test does not take account of the size of the population at risk or the variable length of calendar months. A modification of Edwards' test (by Walter and Elwood) was therefore used in the analysis to allow for unequal time intervals and the assumption of a constant underlying population. The Stata command *seast* was used to compare the observed and expected number of cases per month, and the p-values for the significance of amplitude and for the goodness of fit were calculated [213].

4.3.3 Ethnicity

The ethnic categories used in the questionnaire for ethnicity were based on the ethnic group question in the 1991 Census in England, Wales and Scotland (see table 4.4) [178]. The 1991 census did not include a 'mixed' ethnic group category although LCH cases of mixed race may be reported in the 'Any other ethnic group' category. Confidence intervals were obtained for the numbers in each category. The proportion of ethnic minorities was compared with those reported by the Office for National Statistics using a binomial probability test [214]. This test is suitable for small samples and calculates the probability (p) of the observed number of cases of an ethnic category in the study population given the proportion of ethnicity in the whole UK population. The Stata command *bitesti* was used. It allows summary information to be provided rather than providing the actual data.

Table 4.6 Ethnic group categories (from 1991 Census) [178]

White
Black – Caribbean
Black – African
Black – other, please specify
Indian
Pakistani
Bangladeshi
Chinese
Any Other ethnic group – please specify

4.3.4 Birth weight and gestational age

Although birth weight has been recorded routinely as part of the birth registration process, gestational age has not. Data have been published, however, via Hospital Episode Statistics [215]. A new system for allocating NHS numbers at birth (NN4B) was introduced in 2002 which has facilitated a small amount of birth information, including gestational age, to be collected [216]. In 2005 these data were linked by NHS number to birth registration data held by the Office for National Statistics enabling gestation-specific mortality rates to be published. The birth weight and gestational ages of LCH cases were grouped and compared with 2005 data for England and Wales (E&W). The World Health Organisation definitions for gestational age are shown in table 4.7 [217]. The proportion of live births by birth weight is shown in table 4.8. Comparisons were made using a binomial probability test (*bitesti* in Stata) as described in the previous section. This calculated the probability (p) of the observed number of births in a category in the study population given the proportion of births in that category in the whole population.

Table 4.7 Gestational age definitions (from Moser et al) [217]

Age (weeks)	WHO Description	% live births in E&W (2005)
<37	Pre-term	7.6
37-41	Term	88
>42	Post-term	4
Unknown		0.4

Table 4.8 Percentage of live births by birth weight (calculated from Moser et al)

Weight (grams)	% live births in E&W (2005)
<1000	0.5
1000-1499	0.7
1500-2499	6.3
>=2500	92
unknown	0.3

4.4 Follow up

Cases were followed up one and two years after the date of diagnosis. Short questionnaires (see Appendixes J and K) were sent to reporting clinicians to collect information about vital status, treatment and permanent consequences. The categories for each of these are shown in table 4.9. Where more than one questionnaire was received for a case, data were combined. The date of follow up was taken to be the last date the patient was seen at clinic, or if not stated, the date on which the questionnaire was completed by the clinician. Data from text fields were examined to improve clarity of questionnaire replies, for example, on treatment. Anomalies were checked with the

clinician where possible and definitive responses were taken to be those from the treating consultant oncologist.

Table 4.9 Status, treatment and permanent consequences categories

Status	Treatment	Permanent consequences
Alive, no active disease	Wait and see	Diabetes insipidus
Alive, active disease	Curettage/surgery/ biopsy	Growth failure
Alive, active disease, on treatment	LCH protocol	Anterior pituitary dysfunction
Dead	Other	Hearing loss
		Ophthalmologic problems
		Tooth loss
		Orthopaedic difficulties
		Neurological consequences
		Chronic liver disease
		Chronic lung disease

Patients may have had several types of treatment for their disease but for analysis were grouped according to the main type of treatment received. For example, if treatment was 'LCH protocol' and 'Other', the case was included in the 'LCH protocol' group. Those cases which were reported to have received no treatment, i.e. were 'Wait and see', were checked and were included in the 'Surgery' group if a diagnostic biopsy had been performed. For cases which were likely to have received treatment on LCH protocol (according to the criteria in table 2.3) but where this was not stated on the follow up questionnaire, the original questionnaire data and LCH III clinical trials data were checked.

The status of cases, treatment received and permanent consequences which developed are described. The Mann-Whitney test and Fisher's Exact test were used to assess differences between groups, comparing those with/without disease and those with/without permanent consequences (as described in section 4.3.1).

4.4.1 Disease-free and sequelae-free survival

Survival analysis can be used to study the time to death or other events such as hospital discharge or recurrence of disease. In this study it was used to assess the probability of being without active disease or permanent consequences at two intervals after diagnosis. The analysis allows for the unequal amounts of follow up time contributed by patients (which depends on whether they were diagnosed at the beginning or end of the study period). It also assumes that patients have the same prospects of developing active disease or permanent consequences. The event, i.e. the development of active disease or permanent consequences, may not have taken place in all cases by the end of the follow up period and for these cases the observation time has been censored. The Kaplan-Meier survival method was used to take account of censoring and results are presented as survival 'curves'. The method uses conditional probability, i.e. the probability of being disease-free at the end of a time interval given the probability of being disease-free at the beginning. As events (reactivation or permanent consequences) occur, changes in probability are indicated by steps on the survival curve [218, 219].

The analysis was carried out using the Stata commands *stset*, *sts graph* and *sts list*. These commands describe the number of observations and events, calculate the number of person years at risk, produce survival curves (graphs) and list the events and Kaplan-Meier survival function. Cases which were lost to follow up or for which follow up data were less than six months from diagnosis were excluded. The censor (cut-off) time was the date of the individual's last follow up period.

Disease-free survival and survival without permanent consequences (sequelae-free survival) between different subgroups was assessed. The sub-group categories - sex, age group, type of disease, type of treatment and the time period between symptoms and diagnosis – were as shown in table 4.10. The logrank test was used to test for equality between subgroups [220]. This test calculates the observed and expected number of events for each group (assuming no differences between them) and a Chi-squared test

tests for any significant differences between groups by calculating a p-value. In Stata, the command *sts test* was used.

Table 4.10 Subgroups and categories used in analyses

Subgroup	Categories
Sex	Male, Female
Age group (years)	0-4, 5-9, 10-15
Type of disease	SS, SS multifocal (SS-MF), MS
Treatment	Wait & see, Biopsy/surgery/curettage, LCH protocol, Other
Symptoms to diagnosis period	<12 weeks, >12 to <26 weeks, >26 weeks

Diabetes insipidus (DI) in patients may be regarded as current active disease or as a permanent consequence [98]. For the purposes of sequelae-free survival analysis, if DI was present at diagnosis, the date of the 'event' (permanent consequence) occurring was taken to be the date of diagnosis. However, if a patient with DI at diagnosis subsequently developed other permanent consequences, the event date was the date of follow up. Therefore patients with DI as their only sequela did not contribute to the analysis. The types of permanent consequences are described.

4.5 Mortality

Deaths data were obtained from ONS for the UK and CSO for RoI. Age-standardized Mortality (ASR) rates were calculated using European Standard Populations and the same methods as described in section 4.2.1 for the incidence rate [198].

Chapter 5. Results (1): Ascertainment and incidence of LCH cases

This chapter describes the results of ascertainment of cases and the incidence of LCH in the UK and RoI by age, sex and region. The results of the surveys and patterns of case reporting are also described.

5.1 Survey respondents

BPSU reported that, on average, 92% of paediatric members of the RCPCH returned case report cards to them for our study.

The number of letters sent in each Newcastle mailing is shown in table 5.1. For the reasons described in section 3.2, the list was adjusted after the first mailing and slightly thereafter at each mailing for similar reasons. Replies remained fairly constant over the study period, although the response rate increased as a percentage of letters sent.

Table 5.1 Numbers of letters sent in each Newcastle mail shot

Date sent	Number of letters sent	Number of replies received
November 2003	2229	930
June 2004	1634	936
November 2004	1606	964
June 2005	1587	911

An average of 53% of clinicians responded to each mailing from the Newcastle survey.

The specialty of responding clinicians compared with those on the mailing list is shown in table 5.2. The largest group of clinicians was pathologists (65%) with dermatologists, oncologists and orthopaedic surgeons comprising 21% of the mailing list. As can be seen from table 5.2 the specialties of the respondents were proportional to the specialties on the mailing list.

Table 5.2 Specialty of clinicians on database and response to mailing

Specialty	% on mailing list	% of respondents
Dermatology	8.3	9.7
Endocrinology	4.3	2.9
Haematology	0.1	0.2
Nephrology	0.7	0.2
Neurosurgery	0.2	0.1
Oncology	7.4	6.9
Orthopaedics	6.1	6.3
Paediatrics	0.1	0.2
Paediatric Surgery/Neurosurgery	3.1	2.6
Pathology	65.1	65.8
Radiology	0.2	0.2
Rheumatology	2.4	3
Missing	2	2
Total	100	100

5.2 Case reporting

In response to cases notified by all three sources (BPSU, NCL, CCLG), 358 questionnaires were mailed to clinicians to obtain further information. Of these, there were 217 replies confirming cases. However, questionnaires were not completed for some cases where clinicians were aware that colleagues had already returned a questionnaire. In other cases, clinicians did not have access to full patient history and data was received in a different format, e.g. a pathology report or printed output from a database.

The results of questionnaire mailing are shown in table 5.3. Almost a quarter of questionnaires returned were found to be ineligible and 14% were not returned. After removing adult cases (aged over 18 years), cases diagnosed outside the study period, changed diagnoses, cases reported in error and duplicate reports, 94 cases were identified.

Table 5.3 Response to questionnaire mailing

Category of reply	Number	Percentage
Valid case reports	217	61.0
Changed diagnoses	24	6.7
Notified in error	12	3.3
Diagnosed outside the study period	37	10.3
Adult cases	14	3.9
Not returned	53	14.7
Total	358	100

In the interval between reporting a suspected case and returning a questionnaire, diagnoses were changed in 24 cases. These included patients with the following conditions: haemophagocytic lymphohistiocytosis (HLH), inflammatory responses, intraosseous dermoid, acute myeloid leukaemia, chronic osteomyelitis, Rosai-Dorfman disease, bone cyst, aneurism, and juvenile idiopathic osteoporosis.

Cases diagnosed outside the study period were excluded. Several cases registered with the CCLG were subsequently found to be ineligible because the biopsy on which the diagnosis was made was performed outside the study period.

In addition to 14 questionnaires being returned for adult cases, there were a further 83 reports of adult cases on the Newcastle survey reply slips.

53 questionnaires were not returned. However, 14 of these corresponded to confirmed cases for which data were received from another clinician at the same institution and, similarly, four questionnaires corresponded to ineligible cases.

The 94 cases were confirmed by one or more sources and the frequency is shown in Table 5.4. For 69% there were between 2 and 6 confirmations. Of those with only one notification the majority of cases (18/30) were reported by oncologists with the remainder reported equally by paediatricians or orthopaedic surgeons.

Table 5.4 Frequency of notifications

Frequency	%
1	32
2-3	53
4-6	15

Specialties of clinicians reporting cases are shown in table 5.5. 60% of case confirmations were from paediatricians and oncologists and 27% were from orthopaedic surgeons and pathologists. The remaining 13% were confirmed by radiologists, surgeons and neurosurgeons with single confirmations by an A&E consultant, an endocrinologist and a gastroenterologist.

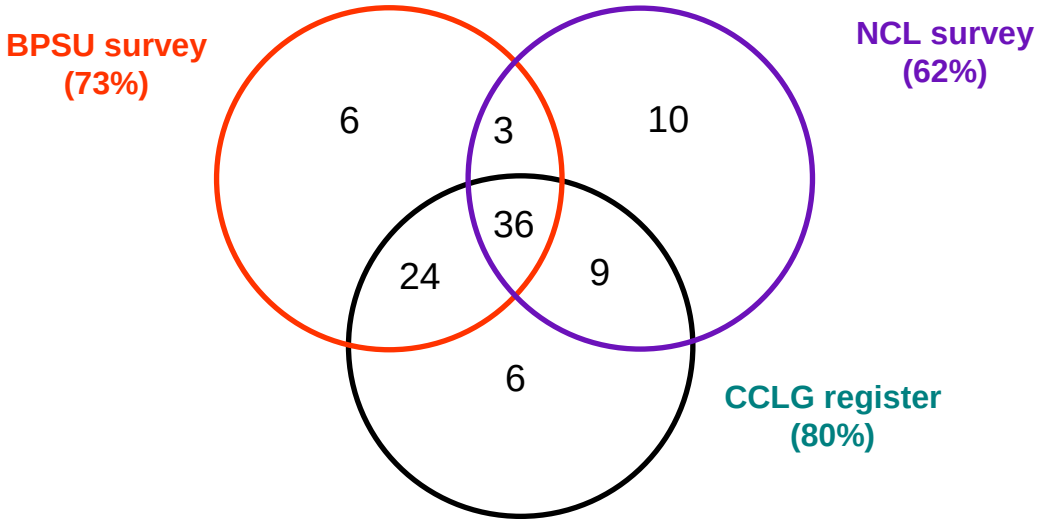
Table 5.5 Specialties of clinicians confirming cases

Specialty	% of cases
Oncology	32.7
Paediatrics	27.6
Pathology	14.7
Orthopaedic surgery	13
Radiology	2.7
Paediatric surgery	2.3
Dermatology	2.3
Neurosurgery	1.8
Paediatric neurosurgery	1.4
Other	1.5
Total	100

5.3 Case ascertainment

The reporting rates for each source were CCLG 75/94 (80%), BPSU 69/94 (73%) and Newcastle University 58/94 (62%) as shown in figure 5.1. No additional cases were identified from deaths data.

Figure 5.1 Number of cases ascertained by each source



5.4 Estimates of completeness of ascertainment by capture-recapture analysis (C-RA)

The completeness of ascertainment was estimated by using Hook and Regal's capture-recapture methods as described in the previous chapter.

5.4.1 Two-source model

Since the CCLG contributed cases but may not have been an entirely independent source the two-source model was used to estimate the completeness of ascertainment by the BPSU and Newcastle surveys only. The number of cases ascertained by each source and the number ascertained by both are shown in figure 5.2.

Figure 5.2 Cases used in two-source model

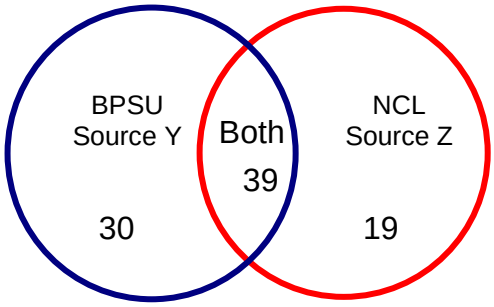


Figure 5.3 Two-source model (from Hook and Regal)

		BPSU: Yes	BPSU: No	
NCL	Yes	39 (a)	19 (b)	Total NCL =58
	No	30 (c)	x	
		Total BPSU =69		

The estimated number of cases is the total of those found by both sources plus those not found by either, i.e. 88+x.

It was estimated that a further 14 cases could be expected giving a total number of 102 (CI: 88.6-115.8) cases rather than the 88 cases reported by the BPSU and Newcastle sources. Case ascertainment for each was estimated to be 69% and 58% respectively; 86% of cases were estimated to be ascertained overall by the two sources. However, this estimate excludes a further six cases which were identified via the CCLG, all of which had been treated by clinicians who had responded to the BPSU or Newcastle surveys.

The estimate was confirmed using Epidat – 102 (CI: 91-113) cases with 86% ascertainment. Case ascertainment (exhaustivity) for each was 68% and 57%. See table 1 in Appendix L.

5.4.2 Three-source model

The Hook and Regal methods were used to estimate the number of missing cases using all sources and to assess the degree of inter-dependence between sources (figure 5.4). The number of cases is shown in table 5.6.

Figure 5.4 Three-source model (from Hook and Regal)

		Source C (BPSU) 1			
		Yes		No	
		Source B (NCL) 2		Source B (NCL) 2	
		Yes	No	Yes	No
Source A (CCLG) 3	Yes	36 (a)	24 (b)	9 (e)	6 (f)
	No	3 (c)	6 (d)	10 (g)	x

N_{obs} = 94

N_1 = 69 A BPSU

N_2 = 58 B NCL

N_3 = 75 C CCLG

With three sources there are eight possible models which estimate the missing and total number of cases. Estimates were calculated by hand for models 2-8 using the Hook and Regal method (table 5.6). As can be seen the estimated number of cases ranged between 95 and 114.

Table 5.6 Rough estimate of number of missing cases

	df*		Model	Estimate of $\hat{x}$	Estimate of $\hat{N}$
1	3		Independent	$\hat{x} = \hat{N} - N_{obs}$ †	
2	2	*Equivalent*	1-2 interactions	1.6	95.6
3	2	*to two*	1-3 interactions	7.5	101.5
4	2	*independent sources*	2-3 interactions	2.4	96.4
5	1	*Two*	1-2, 1-3 interactions	6.6	100.6
6	1	*independent*	1-2, 2-3 interactions	1.5	95.5
7	1	*subsets*	1-3, 2-3 interactions	20	114
8	0		1-2, 1-3, 2-3 interactions	20	114

Sources: 1 = BPSU, 2 = NCL, 3 = CCLG

$\hat{x}$ = unobserved cell; $N_{obs} = 94$; the total population $\hat{N} = \hat{x} + N_{obs}$

† $\hat{N}$ is the solution of $(\hat{N} - N_1)(\hat{N} - N_2)(\hat{N} - N_3) = \hat{N}^2(\hat{N} - \mathbf{N_{obs}})$;

*df = degrees of freedom

The statistical program SAS was then used to solve the quadratic equation for model 1 and calculate models 2-8 as described in Chapter 4. The results of SAS analysis are shown in the following table. They were cross-checked using Epidat, the results of which can be found in Appendix L (table 2).

The estimated number of missing cases ($\hat{x}$) ranged from 1-20 with the estimated total number of cases ($\hat{N}$) ranging from 95-114. Information in tables 5.7 and 5.8 was used to assess which was the best model (described in section 4.1.4).

Table 5.7 Three-source models using SAS

	Model	$\hat{x}$	CI	$\hat{N}$	G^2	df	AIC	BIC
1	Independent	2.43	1.26-4.69	96.43	17.77	3	11.77	9.61
2	BPSU-NCL interactions	1.65	0.64-4.26	95.65	15.31	2	11.31	9.85
3	BPSU-CCLG interactions	7.50	3.52-15.97	101.50	2.33	2	-1.67	-3.23
4	NCL-CCLG interactions	2.38	0.94-6.00	96.38	17.65	2	13.65	12.31
5	BPSU-NCL, BPSU-CCLG interactions	6.67	1.99-22.23	100.67	2.26	1	0.26	-0.51
6	BPSU-NCL, NCL-CCLG interactions	1.5	0.45-4.98	95.5	14.83	1	12.83	12.08
7	BPSU-CCLG, NCL-CCLG interactions	20	2.97-134.73	114	0	1	-2	-2.90
8	BPSU-NCL, BPSU-CCLG, NCL-CCLG interactions	20	4.38-91.29	114	0	0	0	0

$\hat{x}$ = unobserved cell; the total population $\hat{N} = \hat{x} + N_{obs}$
G^2 = goodness of fit; *df = degrees of freedom;
AIC = Aikaike Information criterion; BIC = Bayesian Information Criterion

With reference to the eight models in table 5.7, the first model was excluded as the three sources were assumed not to be independent. The last which has no remaining degrees of freedom was also excluded. In the fourth and sixth models there is evidence that BPSU and CCLG may not be independent as the number of cases appears to be an underestimate. This is also indicated in the two-source restricted estimates (in table 5.8).

Table 5.8 gives a comparison of estimates of the total number of cases using combinations of two sources, i.e. by disregarding the third source (the restricted two-source models in Hook and Regal). Calculations for these were made by hand as described in Chapter 4. The second interaction (BPSU and CCLG), gives a much smaller value for the number of missing cases (and therefore a higher estimate of completeness) than the other combinations suggesting there is positive dependence between these two sources. The two-source restricted estimates were also confirmed by Epidat which in addition produced an estimate of completeness of each model (exhaustivity) (see table 2 in Appendix L).

Table 5.8 Two-source restricted estimates of same population (from Hook and Regal)

Estimates restricted by disregarding the third source

	$\hat{N}_{MLE}$	$\hat{N}_{NUE}$
BPSU versus NCL	102.6	100.1
BPSU versus CCLG	86.25	84.8
NCL versus CCLG	96.6	94.6

MLE maximum likelihood estimator; NUE nearly unbiased estimator

The models in table 5.7 with the best fit are the third, fifth and seventh which have the lowest G^2 value and negative BIC values. However, model 3 (BPSU and CCLG independent of NCL) has narrower confidence intervals, a higher degree of freedom and is a less complex model. Additionally, the interdependence between BPSU and CCLG has been indicated by the results above and coincides with knowledge of the survey lists. The number of missing cases was therefore estimated to be 7 (CI: 3.52-15.97) and the estimated total number of cases was 101.

Analysis using Epidat confirmed the results above although slight differences in the G^2 values resulted in small differences in the AIC and BIC values (see table 1 in Appendix L). The best model estimated 7 missing cases with 101 in total (CI: 94-109). Ascertainment by all three sources was estimated at 93.1% with this model; the estimated individual contributions of each source were CCLG – 74%, NCL – 57% and BPSU 68%.

To summarise, the number of cases ascertained and the estimates of completeness by all methods are shown in table 5.9.

Table 5.9 Summary of estimates of completeness of the survey by all methods

Method	Cases observed	Cases missing	Total expected cases	Confidence Intervals	% Complete
Two-source method – Hook and Regal	88	14	102	89-126.2	86
Two-source method – Epidat	88	14	102	91-113	86
Three-source method – Hook and Regal	94	7	101	–	93
Three-source method – Epidat	94	7	101	94-109	93.1

5.5 Cases ascertained

Data were received on all 94 cases, although questionnaires varied in their completeness. There were 57 boys and 37 girls with a M:F ratio of 1.5:1 and an age range of 0.09-15.1 years. The surveys asked for "children of any age" to be reported. At the upper age range there was a single 15 year old with unifocal (UF) bone disease reported to all three groups and no 16 or 17 year olds. A detailed description of cases is given in Chapter 6.

5.6 Population and incidence rates

5.6.1 Age-standardized incidence rate

From this study population the age-standardized incidence (ASR) of LCH in 0-14 year olds was 4.12 per million per year (CI: 4.11-4.13). The ASR for boys and girls was 4.8 and 3.4 per million per year respectively.

For comparison with other studies incidence rates by sex and age group for those aged 0-14 years are shown in table 5.10. The incidence was 9.9 per million per year (CI: 5.5-16.3) in children less than one year old.

Table 5.10 Incidence rates by age group and sex, per million per year

	IR				
	Age (years)				
	<1	1-4	5-9	10-14	0-14
Boys	10.3	5.7	5.0	2.6	4.7
Girls	9.5	3.9	3.9	1.0	3.2
Both	9.9	4.8	4.5	1.8	4.0
Sex Ratio (M:F)	1.1	1.5	1.3	2.7	1.5

Overall the M:F sex ratio was 1.5:1 which increased to 2.7:1 in the 10-14 years age group.

5.6.2 Age-specific incidence rate

Only one child over 15 years was identified during the study period. The age-specific incidence rate for all cases was therefore only a little lower than the ASR for 0-14 year olds at 3.74 per million per year (CI: 3.02-4.6). If the number of cases (101) estimated by C-RA had been ascertained, the rate would have been 4.02 per million per year (CI: 3.27-4.89).

5.6.3 Regional incidence rates

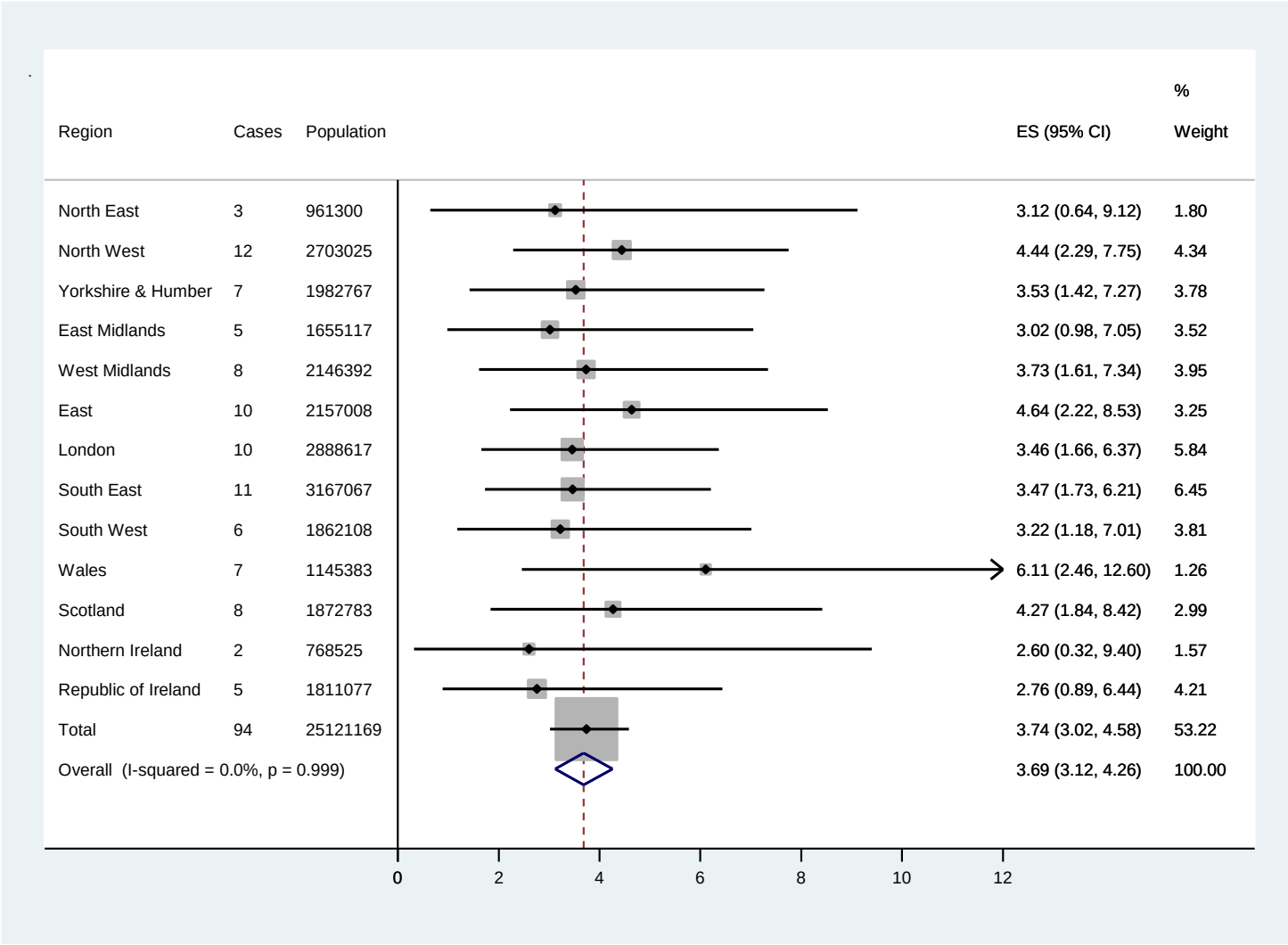
The population studied covers 13 geographical health care regions. Regional age-standardized (age 0-14 years) and age-specific incidence rates (0-15 years) were calculated and the results are shown in table 5.11. With the addition of only one case (in Wales) the rates estimated by each method are similar. Regional ASRs varied from 2.99-5.68 per million per year and age-specific IRs ranged from 2.6-6.11.

Age-specific rates were used to assess heterogeneity between regions using Stata as described in section 4.2.2. The results are shown in figure 5.5.

Table 5.11 Regional age-standardized incidence rates (for cases age 0-14 years) and age-specific rates (for cases age 0-15 years), per million per year

	Age-standardized IR (ASR)			Age-specific IR		
Region	**Cases**	**IR**	**CI**	**Cases**	**IR**	**CI**
Scotland	8	5.34	5.29-5.39	8	4.27	1.84-8.42
Northeast	3	3.79	3.73-3.85	3	3.12	0.64-9.12
Yorkshire & Humber	7	3.71	3.67-3.75	7	3.53	1.42-7.27
Northwest	12	5.08	5.04-5.12	12	4.44	2.29-7.75
West Midlands	8	4.23	4.19-4.27	8	3.72	1.61-7.34
East Midlands	5	3.72	3.68-3.77	5	3.02	0.98-7.05
East	10	4.84	4.80-4.88	10	4.63	2.22-8.53
London	10	3.72	3.68-3.75	10	3.46	1.66-6.37
Southeast	11	5.68	5.64-5.71	11	3.47	1.73-6.21
Southwest	6	3.35	3.31-3.38	6	3.22	1.18-7.01
Wales	6	5.45	5.39-5.51	7	6.11	2.46-12.6
Northern Ireland	2	2.99	2.93-3.05	2	2.6	0.32-9.4
Republic of Ireland	5	3.20	3.18-3.22	5	2.76	0.89-6.44
All	93	4.11	4.12-4.13	94	3.74	3.12-4.26

Figure 5.5 Results of test for heterogeneity for age-specific IRs using Metan



The overall estimate and confidence interval are marked by a diamond. The size of the plotting symbol for each region is proportional to the weight each region contributed in the analysis. The I-squared value (the variation rate in effect size (ES on figure 5.5) due to heterogeneity) was 0.0%; confidence intervals for each region overlapped and the p-value was large (0.99) indicating no statistically significant difference between the rates in each health region.

A Geographic Information Systems (GIS) choropleth map was used to visualise the differences in national and regional age-specific IRs (figure 5.6). The rate is presented as graduated colour with the darker colours representing the higher rates.

The geographical variation in age-specific IRs appears to be random. For example, there is no north to south gradient although the rate was slightly higher in Scotland (4.27) than in the Southeast (3.47), London (3.46) and the Southwest (3.22). The lowest IRs were in Northern Ireland and the Republic of Ireland (2.6 and 2.76 respectively) while the highest rate was in Wales – 6.11 per million per year.

The location of cases based on (partial) postcode of residence at the time of diagnosis is shown in figure 5.7. As can be seen the cases in Wales, which had the highest IR, were widespread.

Figure 5.6 Regional age-specific incidence rates (for cases age 0-15 years), per million per year

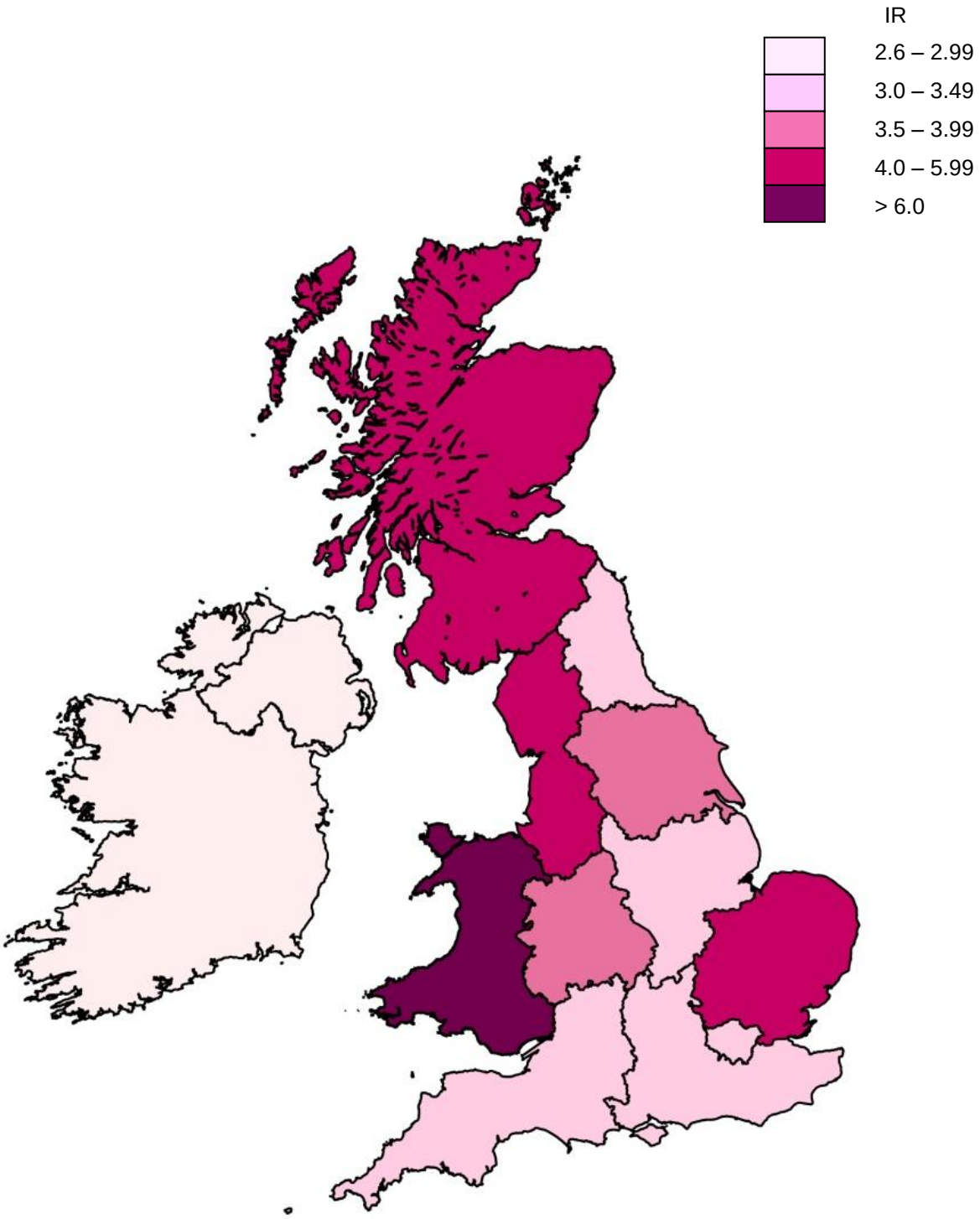
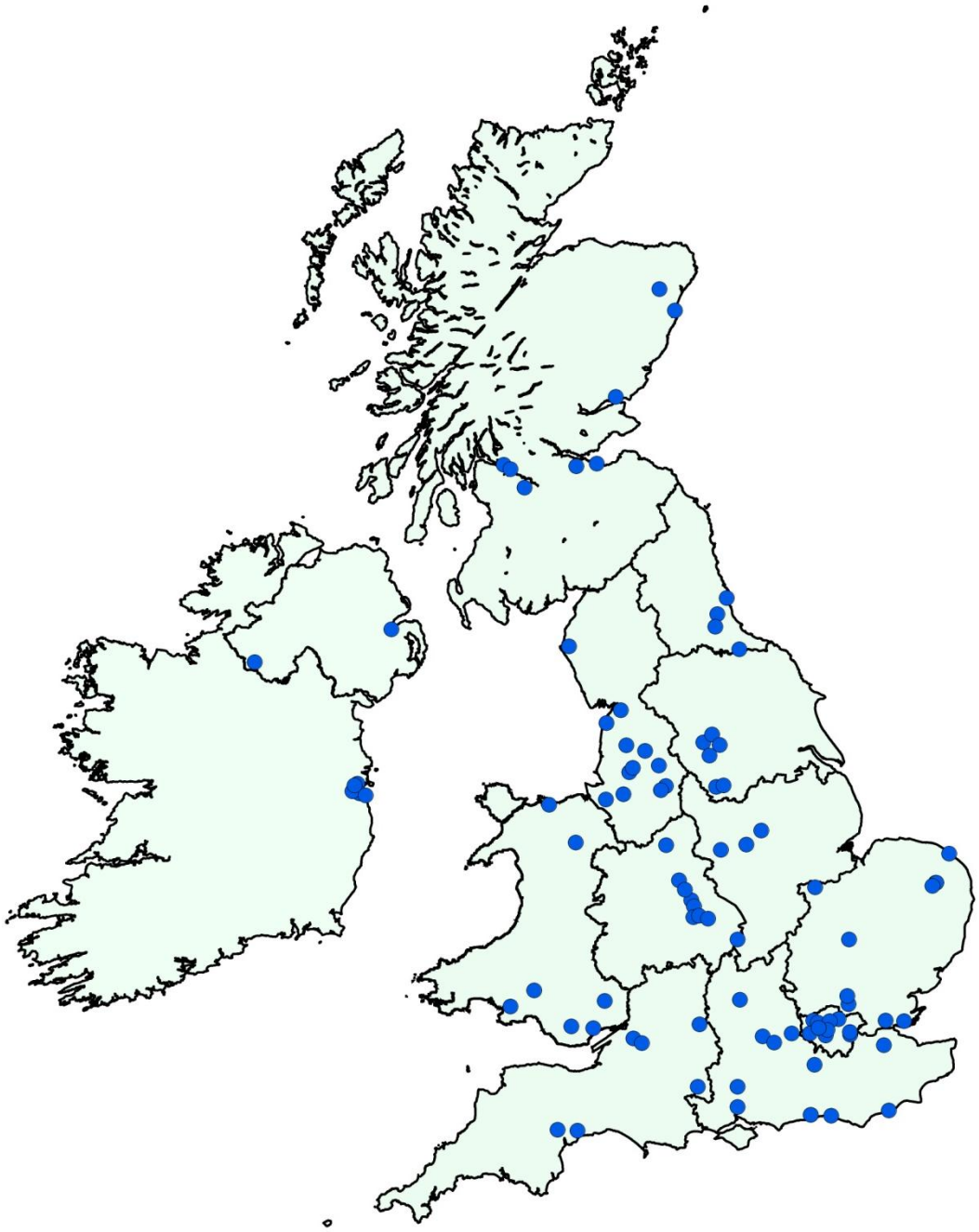


Figure 5.7 Location of cases



5.7 Reporting patterns

5.7.1 Reporting according to disease extent

The pattern of reporting according to disease extent (SS, MS, risk organ involvement) is shown in table 5.12. The table shows those cases uniquely identified and those not identified by each source.

The 10 cases identified uniquely by the Newcastle University survey were all unifocal (UF) bone disease, eight of which were diagnosed and treated at a single national orthopaedic centre.

The two cases of MS disease with risk organ involvement (RO+) uniquely reported to the BPSU were diagnosed post mortem. Of the 25 cases not identified by the BPSU 20 had UF bone disease, but two cases of MS disease without risk organ involvement (RO-) were not reported. Similarly, 16/19 of cases not reported to CCLG were UF bone disease. CCLG were notified of all cases with multifocal (MF) bone involvement and of MS disease, apart from the two cases diagnosed at autopsy.

5.7.2 Comparison with previous CCLG reporting

At the end of the study 89 cases had been notified by the CCLG. However, only 75 of these were included. Of those excluded the date of the biopsy on which the diagnosis was based was outside the study period for nine cases. The others had a change of diagnosis or the diagnosis had not been confirmed, and one was not resident in the UK. The average number of cases per year registered over the two-year study period was 37.5 and was similar to the average of those reported to the CCLG in the previous 11-year period (36.7 cases per year, range 29-52) as shown in Chapter 1 (figure 1.3).

Table 5.12 Pattern of case reporting

Source	Total Cases	SS			MS	
		Bony		Other	RO+	RO-
		UF	MF			
Total	94	53	10	6	7	18
Uniquely identified by						
BPSU	6	3	–	1	2	–
Newcastle University	10	10	–	–	–	–
CCLG	6	4	1	–	–	1
Not identified by						
BPSU	25	20	2	1	–	2
Newcastle University	36	19	3	3	5	6
CCLG	19	16	–	1	2	–

RO = risk organ involvement

5.7.3 Incidence by type of disease

For comparison with other studies, incidence rates were calculated by age group and type of disease for those aged 0-14 years, i.e., 93/94 cases identified, as shown in table 5.13.

Table 5.13 Incidence rates by age group and type of disease (per million per year, aged 0-14 years)

Age group (years)	SS				MS			Total
	Bony		Other	All	RO+	RO-	All	
	UF	MF						
<1	2.0	–	1.3	3.3	4.6	2.0	6.6	9.9
1-4	2.5	0.9	–	3.4	–	1.4	1.4	4.8
5-9	2.8	0.5	0.4	3.7	–	0.8	0.8	4.5
10-14	1.5	0.1	0.1	1.7	–	0.1	0.1	1.8
0-14	2.2	0.4	0.3	2.9	0.3	0.8	1.1	4.0

The highest rate of MS disease was in those under one year of age and rates declined with increasing age. With regard to SS disease the rate in infants was half that of MS disease. Rates of SS disease were thereafter similar in other age groups with a lower rate in 10-14 year olds. The highest rate of those with MF bone disease was in the 1-4 years age group.

Incidence rates by sex and type of disease are shown in table 5.14. In both sexes MS disease rates decreased with age, the highest rate being in males under one year of age (7.7 per million per year). The rate of SS disease was highest in females aged less than one year (three females compared with two males); the highest rate in males was in the 1-4 years age group.

Table 5.14 Incidence by sex and type of disease (per million per year, aged 0-14 years)

Age group (years)	Male			Female			Total
	SS	MS	Total	SS	MS	Total	
<1	2.6	7.7	10.3	4.1	5.4	9.5	9.9
1-4	4.0	1.7	5.7	2.8	1.0	3.8	4.8
5-9	3.8	1.3	5.1	3.7	0.3	4.0	4.5
10-14	2.3	0.2	2.6	1.0	–	1.0	1.8
0-14	3.3	1.42	4.7	2.5	0.7	3.2	4.0

Chapter 6. Results (2): Descriptive epidemiology and analyses of outcome

As reported in the previous chapter, 94 cases of LCH were ascertained. There were 57 boys and 37 girls with a M:F ratio of 1.5:1. A detailed description of these cases follows including spectrum of disease, time taken to diagnosis, birth and other associated factors, and ethnicity. The status of cases after the first and second follow up periods and permanent consequences are also described. In addition, disease-free survival and survival without permanent consequences are assessed and mortality estimated.

A list of the 94 cases and those included in both follow ups are shown in Appendix M. As patient names were unknown the list is anonymous. However, sex, dates of birth and dates of diagnosis of cases are given with type of disease and their inclusion or exclusion in the follow ups.

6.1 Diagnosis

Diagnostic biopsies were reported in 78 cases. The basis of diagnosis is shown in table 6.1. Eleven bony lesions and two cases with isolated diabetes insipidus (DI) were diagnosed by typical radiological appearance. For one case of bone disease the basis of the diagnosis was not stated. Two young children with MS LCH were only diagnosed at autopsy.

Table 6.1 Basis of diagnosis of cases

Basis of diagnosis	Cases
Biopsy	78
Radiology	13
Post mortem	2
Not known	1
Total	94

6.2 Symptoms and presentation

Not all questionnaires recorded the first symptoms (87/94) or the date on which they appeared (85/94). However, the frequency of symptoms reported is shown in table 6.2. One case was found incidentally following a skull X-ray and nine cases presented after a fall or minor trauma. Seven of these had SS bone disease and the other two had MS RO- disease – of skin and bone, and skin, bone and nervous system. 'Other' symptoms included fever or infections, hepatosplenomegaly, lymph node enlargement, colitis, poor weight gain and diarrhoea/vomiting. Infections or fever occurred mainly in those with MS disease (5/8) cases. 26 cases had more than one symptom.

Table 6.2 Frequency of presenting symptoms

Presenting symptoms	Number of cases
Pain or restricted movement	39
Swelling or lump	29
Rash or lesion	14
Polyuria/polydipsia	6
Ear discharge	5
Proptosis or swelling above the eye	5
Other	11

The patient's initial consultation is recorded for 64 cases as shown in table 6.3. For 78% of these the first consultation was with a GP and 16% went to Accident and Emergency (A&E). Two children were already under the care of a consultant for cancer treatment and neurological problems respectively. One child with disseminated congenital LCH remained in Paediatric Intensive Care from birth.

Table 6.3 Initial consultation of cases

Initial consultation	Number of cases
GP	50
A&E	10
Consultant	3
Optician	1
Total	64

However, in addition to those cases that were referred via A&E (10), a further 17 cases were first referred to their local hospital services including non-paediatric services.

6.3 Time to diagnosis from first symptoms

The time from first symptom to diagnosis was reported for 85/94 cases and is detailed in table 6.4. The cases for which there was no information all had SS bone disease. The median time was 11.5 weeks. There is wide variation with the longest median time to diagnosis in patients with non-bony SS disease and the shortest median time in patients with MS RO+ disease. The longest time to diagnosis, 170 weeks, was in a patient with a single bony lesion. There was no significant difference in the time from symptoms to diagnosis between SS, SS multifocal (SS-MF) and MS groups (p=0.12), by sex (p=0.15) or by age group (p=0.28).

Table 6.4 Number of weeks from first symptom to diagnosis by type of disease

Type of disease	Median (weeks)	Range (weeks)
SS	10	0.5–170
Bone	10	0.5–170
UF	10	0.5–170
MF	13	0.5–65
Other	28	6.7–37
MS	17	2.5–149
RO^+	9	3.1–27
RO^-	20	2.5–149

Table 6.5 shows the number of cases diagnosed by the interval from first symptoms to diagnosis. Overall, 45% of cases were diagnosed in less than twelve weeks from the first symptoms. Those diagnosed in under four weeks comprised seven SS bone cases, two of which were MF, and two MS cases (one RO+ and one RO-). Those who took longest to be diagnosed, over a year, had persistent skin rash, recurrent ear infections and multiple visits to their GP with back or leg pain.

Table 6.5 Frequency of cases by time from first symptom to diagnosis

Interval from symptoms to diagnosis (weeks)	Number of cases
<4	9
4-11	34
12-25	20
26-51	14
>=52	8
Not known	9
Total	94

6.4 Spectrum of disease

Table 6.6 shows cases by type of disease, sex and age at diagnosis. Overall 69/94 (73%) of cases had SS disease and 25 (27%) had MS disease; 18 were RO- and seven were RO+. There were two cases of isolated skin disease and the 'Other' cases were two each of lymph and diabetes insipidus.

Table 6.6 Cases of LCH by type of disease, sex and age at diagnosis

LCH system	Number	Sex		Median age at diagnosis (years)	Age range (years)
		M	F		
SS	69	40	29	6.7	0.12–15.1
Bone	63	36	27	6.7	0.38–15.1
UF	53	31	22	7.3	0.38–15.1
MF	10	5	5	4.8	1.58–13.63
Skin	2	1	1	0.54	0.12–0.96
Other	4	3	1	9.0	8.8–10.0
MS	25	17	8	1.2	0.09–14.8
RO^+	7	5	2	0.7	0.09–0.9
RO^-	18	12	6	3.2	0.32–14.8

6.4.1 Age at diagnosis and sex

The age range of cases was 0.09-15.1 years. Table 6.6 shows the median age at diagnosis by type of disease. At the upper age range there was a single 15 year old male with UF bone disease and no 16 or 17 year olds. The median age at diagnosis was 5.5 years which differed slightly between boys (6.1 years) and girls (5.0 years).

The number of cases by age and sex, and by age and system involved are shown in figures 6.1 and 6.2. There was a significant difference in age at diagnosis among SS, SS-MF and MS cases – medians 6.7, 4.8 and 1.2 years respectively (p=0.001). The youngest children (less than one year of age) at diagnosis were those with skin and MS RO+ disease, the medians being 0.54 and 1.2 years respectively. There was an age difference between those with UF and MF bone disease, the medians being 7.3 and 4.8 years respectively. The oldest children had SS UF bone disease or disease of pituitary or lymph.

16% cases were diagnosed aged less than one year; 30% were 1-4 years, 37% were 5-9 years and 17% were aged 10-15 years at diagnosis.

Overall the M:F ratio was 1.5:1. There was no significant difference in age at diagnosis between the sexes (p=0.2). The M:F ratio in the MS group was 2.1:1 with the RO+ cases being diagnosed at the younger median age of 0.7 years compared to 3.2 years in the RO– patients.

Figure 6.1 Number of cases by sex and age at diagnosis

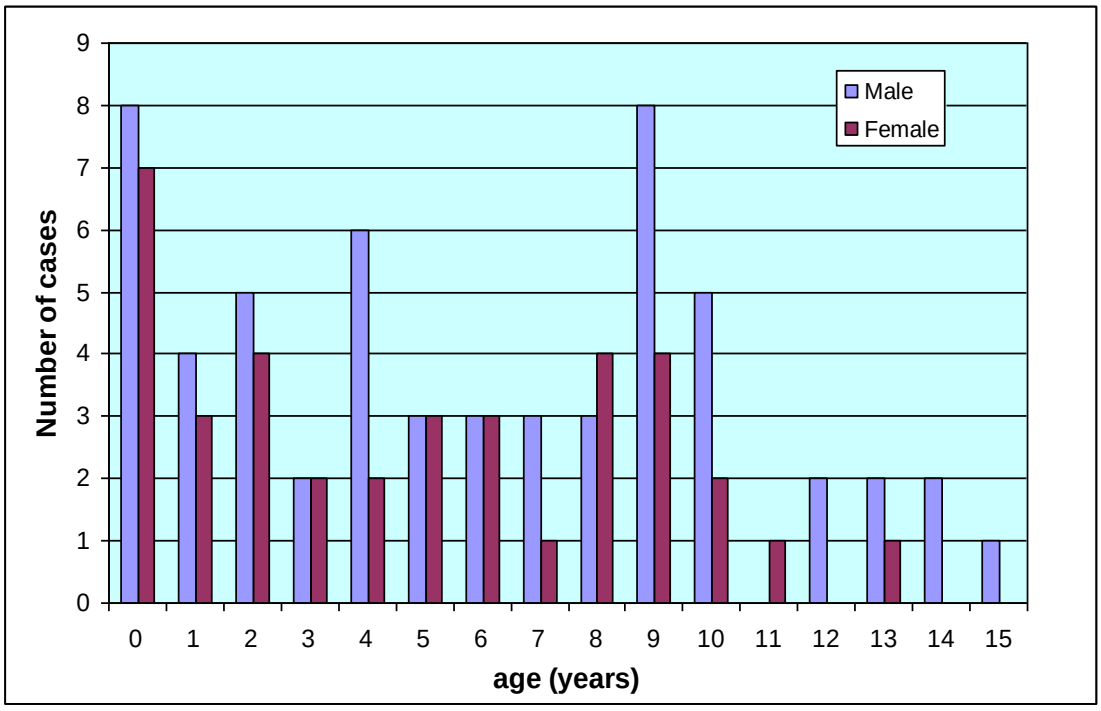
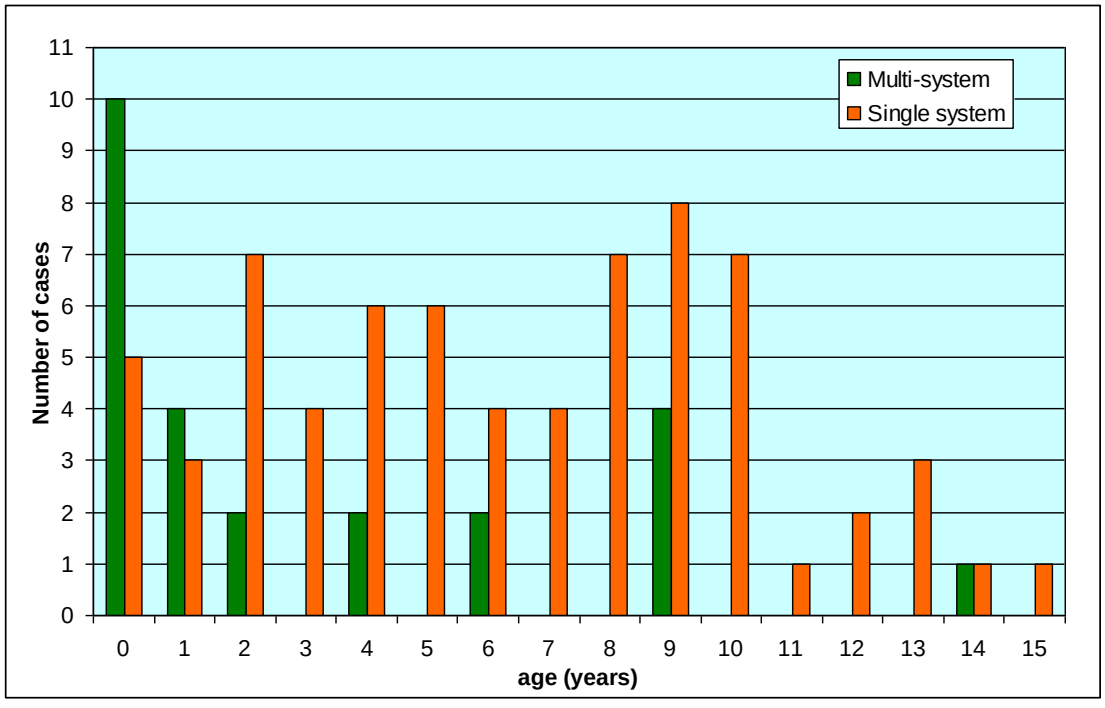


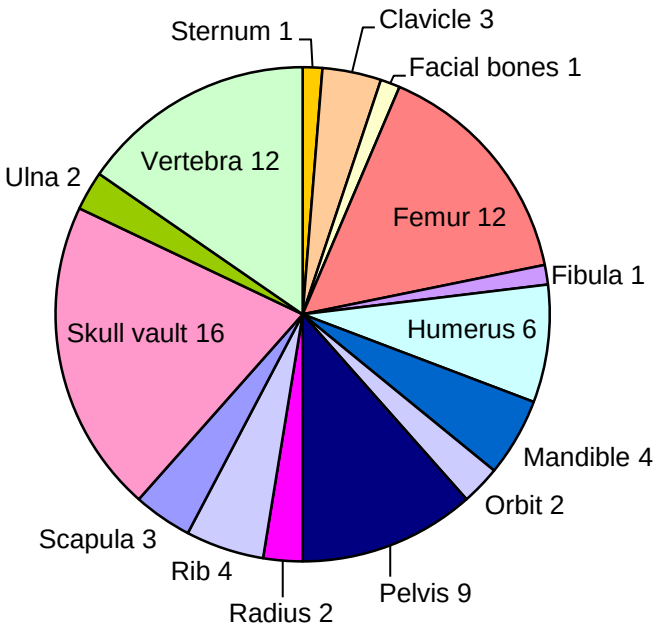
Figure 6.2 Number of cases by age and system involved



6.4.2 Single system disease

Of the 69 cases with SS disease, 53 were cases of UF and 10 were of MF bone disease. The remainder comprised two cases each with skin, pituitary (diabetes insipidus (DI)), and lymph node involvement. The sites of SS bone disease and their frequency are shown in figure 6.3. 28% of UF cases were of skull, the next most common sites being pelvis (15%), vertebra (13%) and femur (9%). Of the MF bone cases 7/10 had femur involvement and 5/10 had vertebral involvement. Only one of the MF bone cases had skull involvement. The UF bone cases were diagnosed at a median age of 7.3 years compared with 4.8 years for MF bone cases and 0.54 years for those with skin disease.

Figure 6.3 Pie chart showing the frequency and distribution of unifocal and multifocal bone disease



6.4.3 Multi-system disease

Of the 25 MS cases, 18 were RO-, the most common sites being bone, skin, DI, nervous system and ear. The sites of RO- disease and their individual frequency are shown in figure 6.4. Combinations of the sites involved were examined to see if there were any particular clusters of disease. The frequency of these combinations is shown in figure 6.5.

Figure 6.4 Pie chart showing the frequency and distribution of systems involved in MS RO- cases

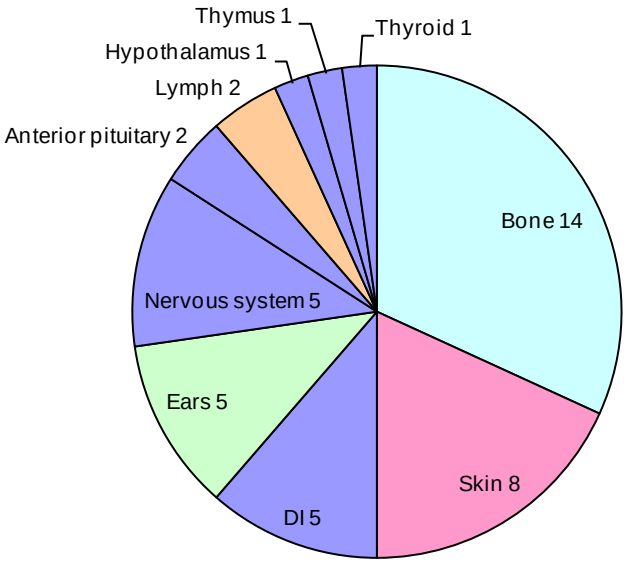
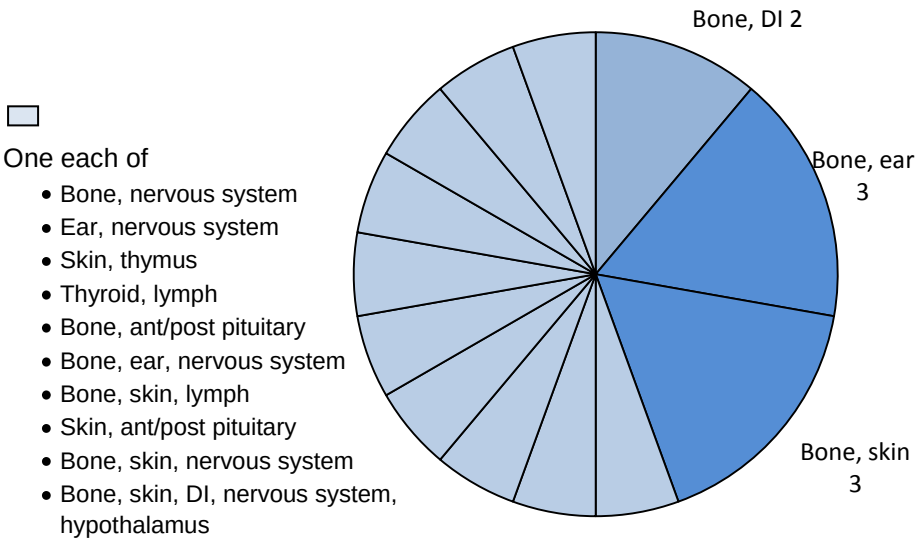


Figure 6.5 Pie chart showing the frequency of combinations of sites involved in MS RO- cases



As can be seen in figure 6.5, most RO- cases had a unique combination of disease sites although there were multiple bone cases with skin or ear disease or diabetes insipidus.

Among the seven RO+ cases, the combinations of organs involved in each case were unique. The most common sites were skin, liver, lung and spleen. Whereas all RO+ cases had skin disease, only one had bony involvement.

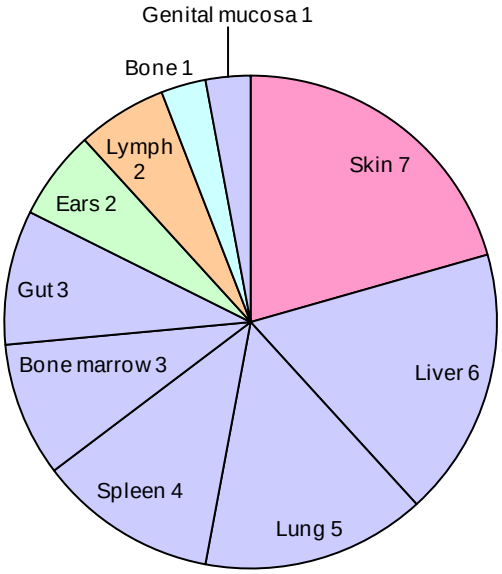
The frequency of risk organ involvement (liver, lungs, bone marrow or spleen) in the seven RO+ cases is shown in table 6.7

Table 6.7 Frequency of risk organ involvement in MS RO+ cases

No. of systems	No. of RO+ cases
1	1
2	3
3	1
4	2

The case with only one risk organ involved had lung, bone and skin disease. However, lung disease was only diagnosed post mortem.

Figure 6.6 Pie chart showing the frequency and distribution of systems involved in MS RO+ cases



6.5 Seasonality

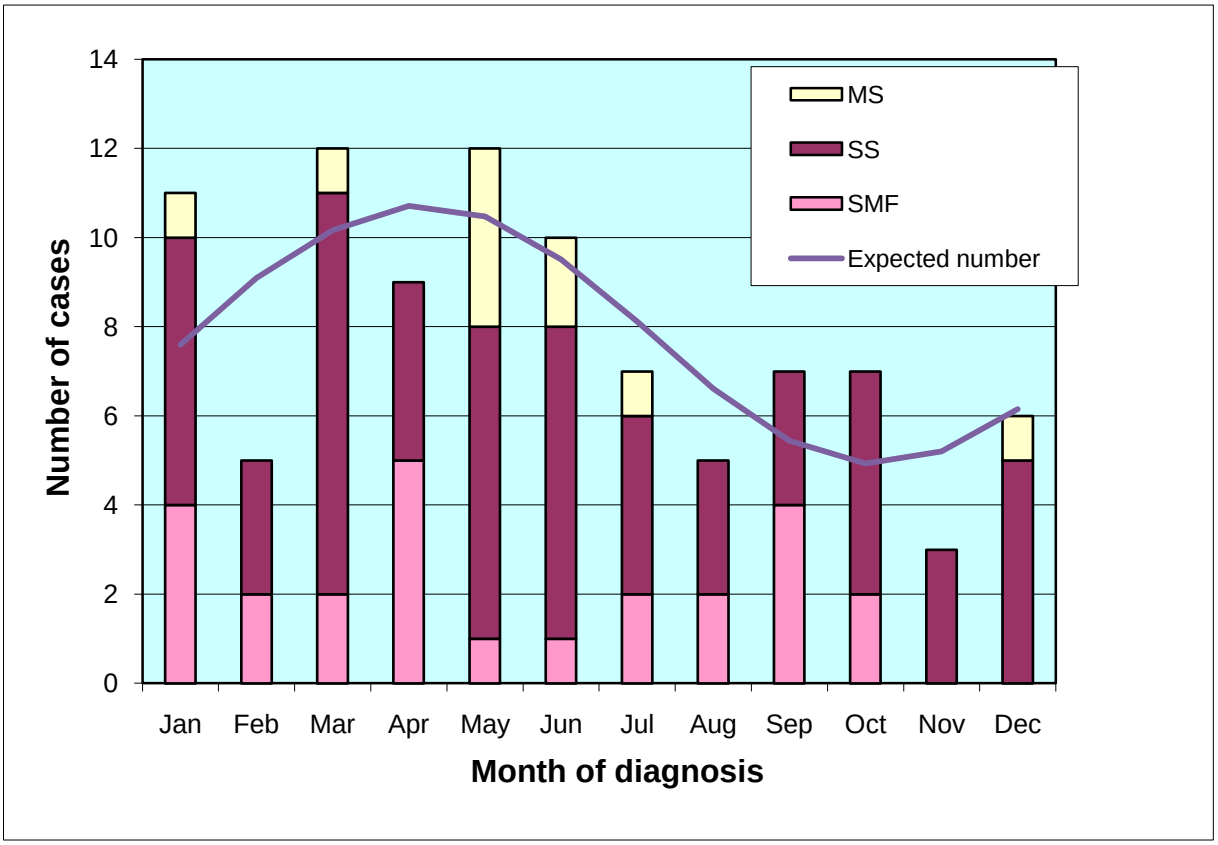
Dates of birth and diagnosis were recorded for all cases; the month of first symptom was reported for 85 cases. The results of the seasonality tests by month of birth, month of first symptoms and month of diagnosis are shown in table 6.8 with the observed and expected numbers per month.

Whilst there was no evidence of seasonality of birth (p=0.94) or of first symptom (p=0.86), there was a significant association with month of diagnosis (p=0.04). A higher number of cases than expected (under an assumption of no seasonal effect) were diagnosed between March and June. The observed number of cases was actually slightly lower than the expected number in April, although this was the month with the maximum value of the fitted curve. The amplitude was 37%, i.e. the expected value for April was 37% above the mean value for the whole year. The goodness of fit for this test was 0.8 (i.e. a good fit). The month of diagnosis of cases by type of disease is shown in figure 6.7 which also shows the fitted curve with peak in April.

Table 6.8 Observed and expected number of cases in seasonality tests

Test by	Month of birth		Month of first symptom		Month of diagnosis	
Month	Observed	Expected	Observed	Expected	Observed	Expected
January	7	8.18	6	7.65	11	7.59
February	9	8.25	7	7.47	5	9.09
March	11	8.21	7	7.21	12	10.16
April	4	8.07	10	6.89	9	10.71
May	13	7.87	5	6.63	12	10.47
June	4	7.65	6	6.49	10	9.51
July	8	7.49	6	6.51	7	8.12
August	7	7.42	6	6.68	5	6.61
September	4	7.46	10	6.97	7	5.44
October	15	7.59	6	7.27	7	4.93
November	9	7.8	8	7.54	3	5.2
December	3	8.01	8	7.67	6	6.15
Total	94		85		94	

Figure 6.7 Month of diagnosis of cases by type of disease



6.6 Ethnicity

The number of cases by ethnicity and sex is shown in table 6.9. Overall 75 children were white caucasian (80%, CI: 70-87%), 13 (14%, CI: 7.6-22%) were of mixed or other ethnicity and in 6/94 cases ethnicity was not reported (6%, CI: 2.4-13%). The proportion of those with mixed or other ethnicity in the general population is 7.9% [214]. Where ethnicity was reported (in 88 cases), the proportion of mixed or other ethnicity was significantly different from the proportion of ethnic minorities in the whole population (p=0.027). However, the probability of mixed or other ethnicity cases in all 94 cases was not statistically significant different from the probability of ethnicity in the whole population (p=0.051).

Table 6.9 Number of cases by ethnicity and sex

Ethnicity	Number of Males	Number of Females	Total number of cases
White	46	29	75
Black – Caribbean			
Black – African	1	0	1
Black – other			
Indian/Pakistani	2	0	2
Bangladeshi	1	0	1
Chinese			
Other or mixed race	4	5	9
Not known	3	3	6
Total	57	37	94

6.7 Birth-associated factors

There were three sets of twins with one of each pair affected. One was born prematurely and after many neonatal complications was diagnosed with UF skull vault disease aged one year. The two other cases (2%: CI: 0.2-7%) were reported to have been conceived by IVF. One developed UF vertebral bone disease at age 11 years and the other had Congenital Self-healing Histiocytosis (Hashimoto-Pritzker disease).

There were three other congenital cases – a boy with proptosis, a female with MS disease (skin and bone), and a boy with RO+ disease and multiple gastric atresias who died aged one month. No children of consanguineous parents were reported.

6.7.1 Birth weight

The birth weights of 60/94 cases were reported and were comparable with live births in the general population as shown in table 6.10. The range was 0.99-4.5kg and the median was 3.3kg. There was no difference in birth weights between those with SS or MS disease (p=0.35).

Table 6.10 Percentage of live births by birth weight

Weight (grams)	% births in study group (60)	% births in UK population
<1000	1.6	0.5
1000–1499	0	0.7
1500–2499	6.6	6.3
>=2500	91.6	92

The proportion of children with a birth weight of <1000 grams was slightly higher in our study group but this was not significantly different from that in the UK population (p=0.26).

6.7.2 Gestational age

Gestational ages were recorded for 82/94 cases and were comparable with those in the general population as shown in table 6.11. The range was 27.5-43 weeks and the median was 40 weeks. There was no difference in gestational age between those with MS or SS disease (p=0.58). Although the proportion of pre-term births was higher in the study group this was not significantly different from the proportion in the UK population (p=0.13).

Table 6.11 Gestational age

Age (weeks)	Description	% in study group (82)	% of live births in UK population (2005)
<37	Pre-term	12.2	7.6
37–41	Term	83	88
>42	Post-term	4.9	4

6.8 Associations with other factors

6.8.1 Cancers

Two children had medulloblastoma. In one case the tumour preceded the diagnosis of SS, UF bone disease. The second was diagnosed six months after SS, UF bone disease which had not required treatment.

6.8.2 Co-morbidities

One child had partial Trisomy 3. Other conditions included seizure disorder and developmental delay in one child and pneumothorax and necrotizing enterocolitis in the preterm twin. Juvenile xanthogranuloma was also diagnosed in a child with MS disease.

6.8.3 Maternal and family history

Among maternal history during pregnancy, one of each of the following conditions were reported: Darier's disease (a rare, autosomal dominant skin disorder – the affected child had MS RO+ disease diagnosed at autopsy), hypothyroidism, epilepsy, melanoma, thalassaemia, asthma/psoriasis, diabetes/epilepsy and cholestasis. With regard to infections, one mother was receiving penicillin for an itchy rash and another had a Streptococcus B infection around delivery.

6.9 Deaths

There were three deaths among the 94 cases ascertained, all male and with MS RO+ disease. One of these was a baby with congenital disseminated LCH who died aged one month. The second child died at age 10 months. Both of these children were diagnosed post mortem. The third child was diagnosed with skin disease but died at nine months of age and was found to have MS LCH post mortem. Although LCH was the recorded cause of death on the death certificate there may have been other contributing factors in this case.

6.10 First year follow up

Surviving cases (91) were followed up one year after the date of diagnosis. For five SS bone cases, follow up forms were not returned and the date of the last follow up at clinic was less than six months from diagnosis; these were excluded from analysis. Of

the 86 cases assessed, the median number of months from diagnosis was 1.3 years (range 0.5-3.3 years). There were 51 males and 35 females (ratio 1.5:1) which comprised 18 MS RO-, 4 MS RO+, 48 SS bone, 10 MF bone and 6 other SS cases.

6.10.1 Status at one year

The status of these 86 patients was as shown in table 6.12. 75 were alive with no active disease and 11 children had active disease – four SS UF bone and seven MS cases. There were no deaths. The SS diabetes insipidus (DI) cases were reported by clinicians as not having active disease and grouped accordingly.

Table 6.12 First year follow up status by type of disease

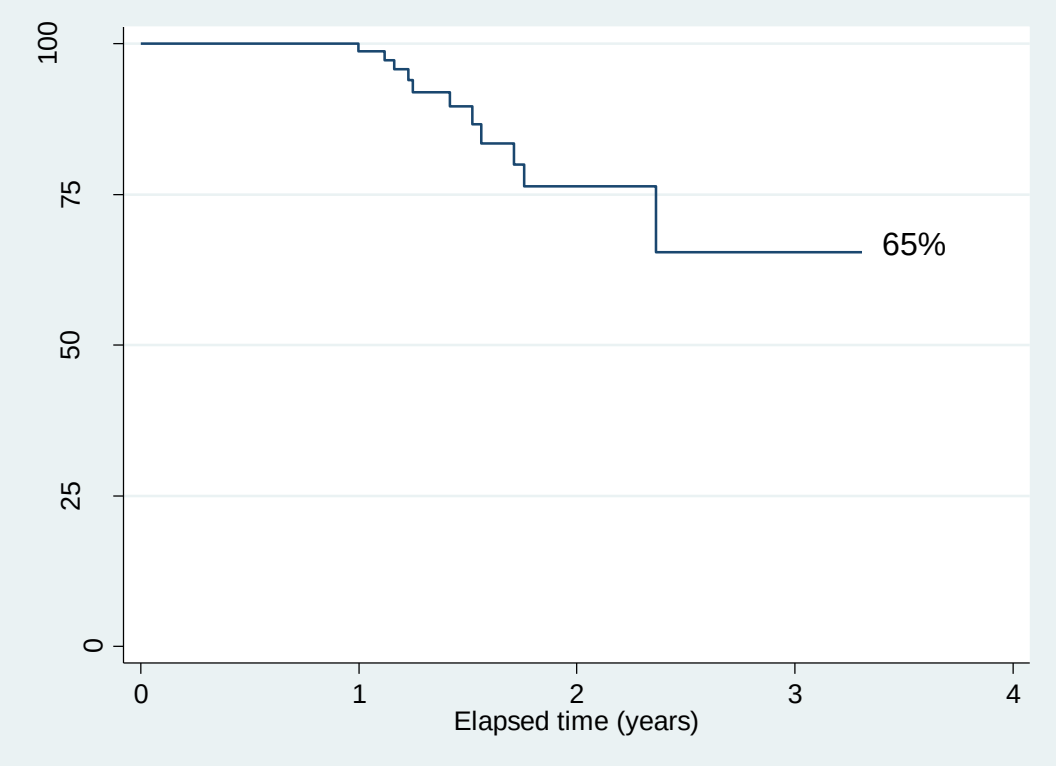
Status	SS (all)	UF Bone	MF Bone	SS Other	MS RO–	MS RO+	Total (91)
Alive, no active disease	61	44	10	6	12	3	75
Alive, active disease	2	2	0	0	4	0	6
Alive, active disease, on treatment	2	2	0	0	2	1	5
Dead	0	0	0	0	0	0	0
Lost to FUP or excluded	5	5	0	0	0	0	5

There was no significant difference in the age at diagnosis or in the time from symptoms to diagnosis between those with and without active disease (p=0.26 and p=0.38 respectively), nor was there a difference by sex (p=0.5). However, there was a difference by type of disease (SS, SS-MF and MS) (p=0.01) and treatment (p=0.05). There were a larger number of MS cases and those treated on LCH protocol than expected.

Kaplan-Meier survival analysis was used to assess active disease-free survival at one year. There were a total of 129 person years of follow up. Overall there was a 65% probability of active disease-free survival after 3.3 years (CI: 38%-83%) as shown in

figure 6.8. However the confidence intervals were very wide and the probability of being disease-free at two years which includes 10/11 cases was 76% (CI: 59%-87%).

Figure 6.8 Overall probability of having no disease at first follow up



The logrank test was used to assess disease-free survival between different subgroups based on sex, age group, type of disease, type of treatment and the time period between symptoms and diagnosis (figures 6.9 to 6.13). Data for each subgroup were available for all 86 cases except for the time period between symptoms and diagnosis where the date of first symptoms was missing for six (SS bone) cases. P-values are shown and the numbers in each subgroup are given in brackets on each graph.

There was no difference in the probability of being disease-free between any of these subgroups except by type of disease. There was a significant difference in disease-free survival between MS and SS disease cases (figure 6.11). The probability of having active disease was 55% in MS cases which was 13% less than for SS cases (p=0.03).

Figure 6.9 Probability of having no disease by sex at first follow up

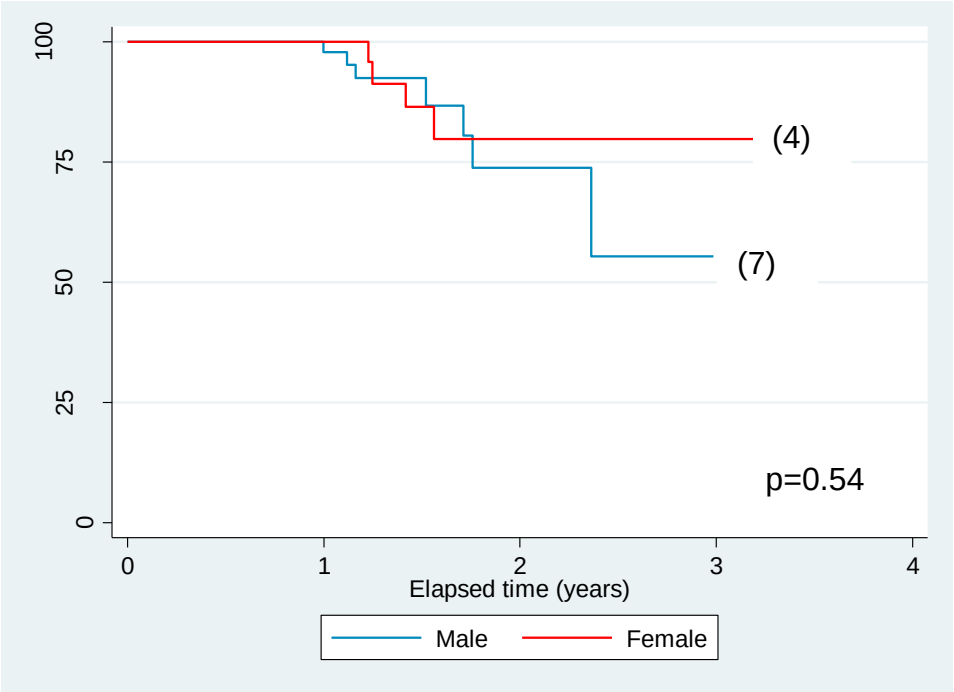
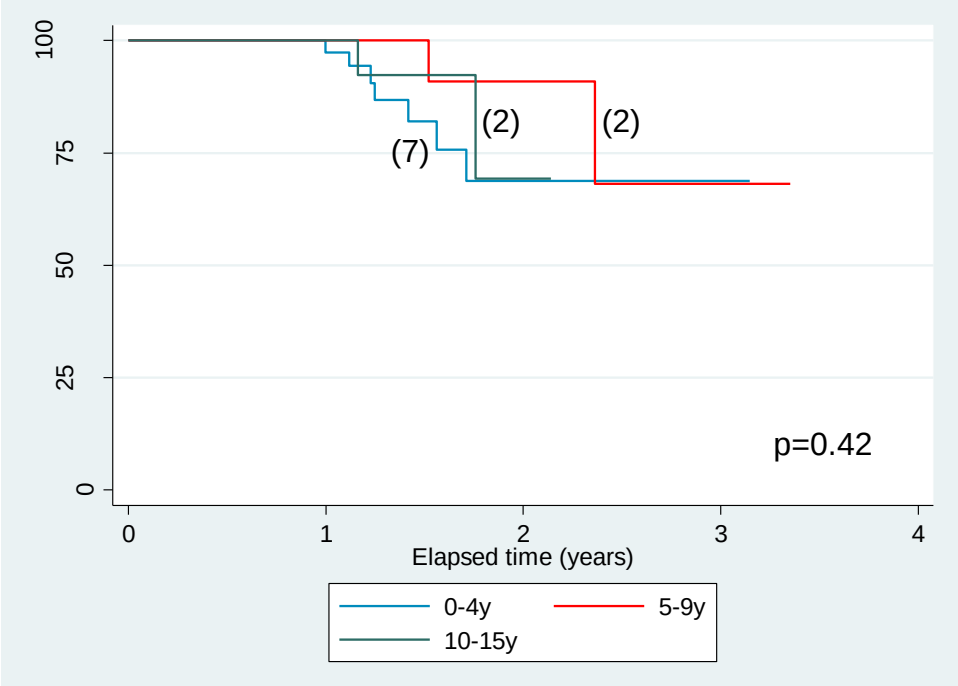


Figure 6.10 Probability of having no disease by age group at first follow up



The number of cases in each subgroup is shown in brackets

Figure 6.11 Probability of having no disease by type of disease at first follow up

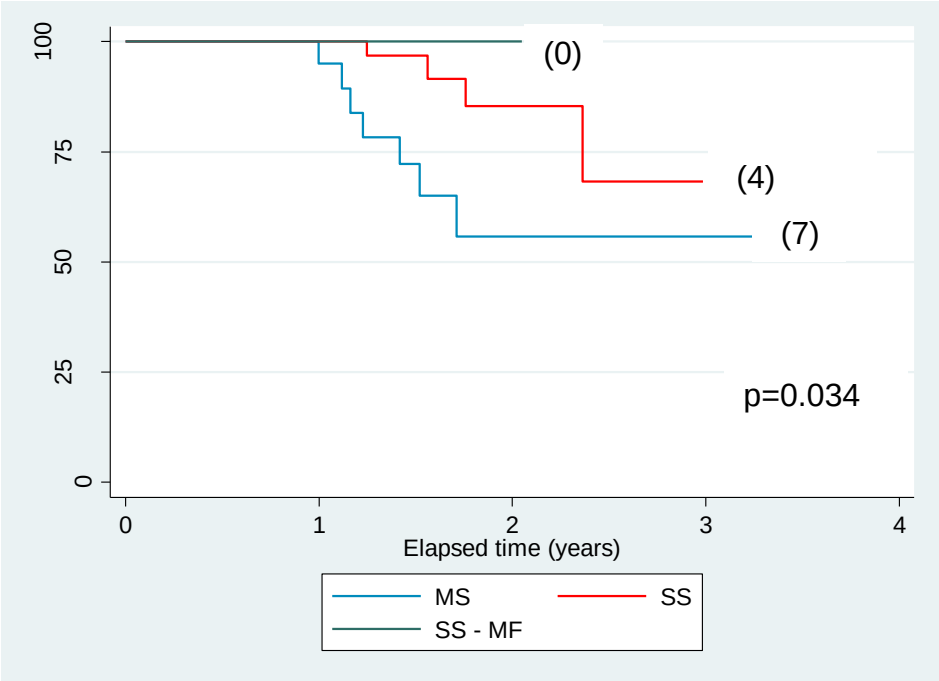
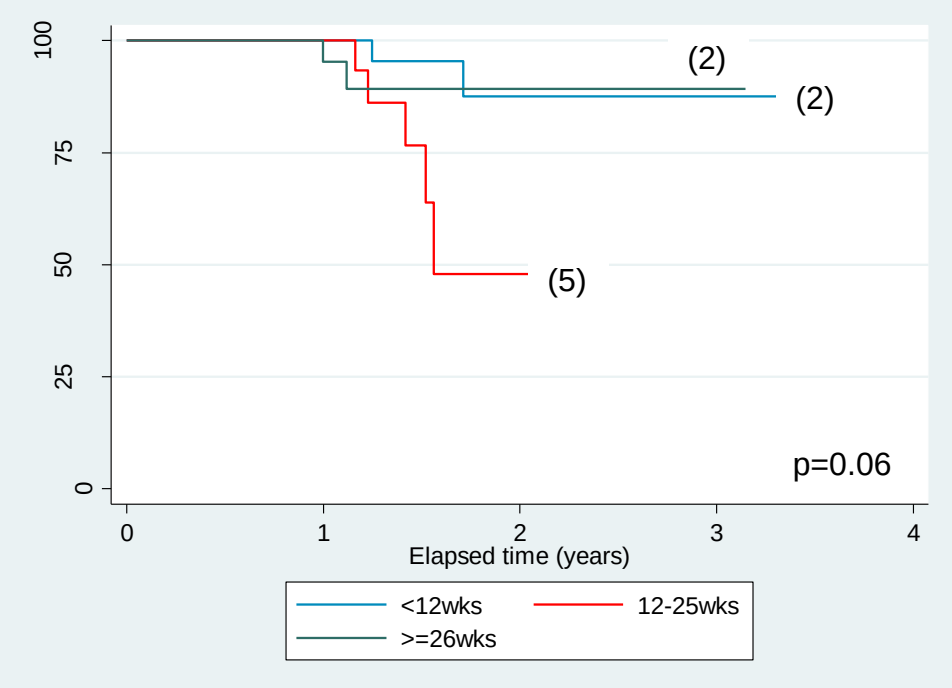
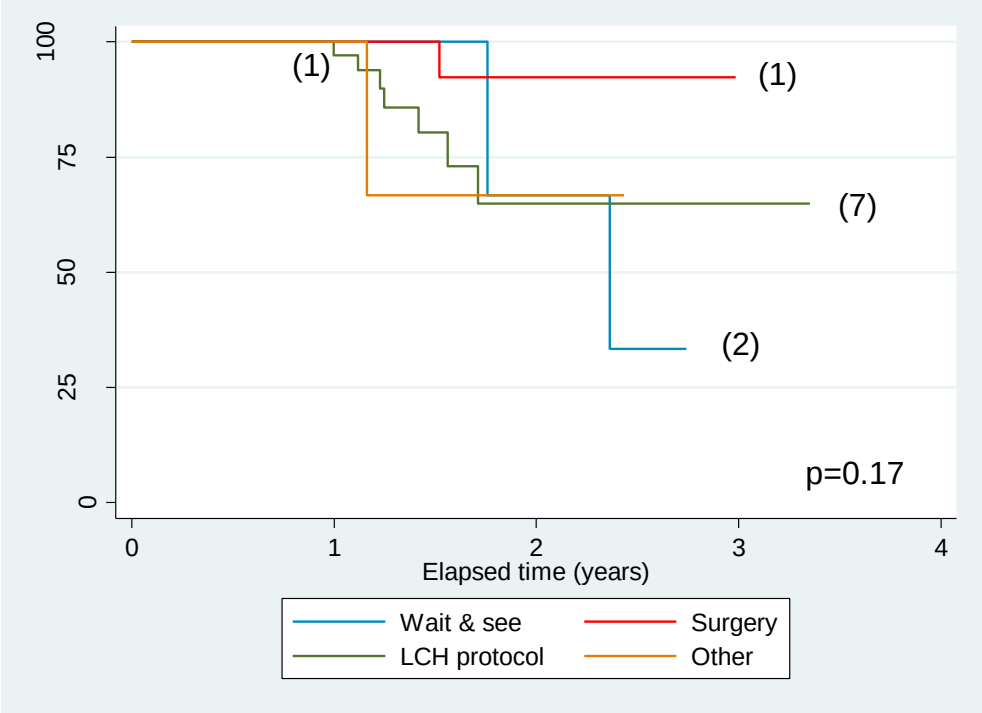


Figure 6.12 Probability of having no disease by time from symptoms to diagnosis at first follow up



The number of cases in each subgroup is shown in brackets.

Figure 6.13 Probability of having no disease by type of treatment at first follow up



The number of cases in each subgroup is shown in brackets.

6.10.2 Treatment

Treatment during the first year by sex and system involved is shown in table 6.13. 12% of cases did not receive treatment; 40% had a biopsy, curettage or surgery and 43% were on LCH protocol or received other chemotherapy. Four children on protocol had additional chemotherapy.

Table 6.13 Treatment at first follow up by sex and system involved

	Male			Female			
Status	**SS**	**MS RO–**	**MS RO+**	**SS**	**MS RO–**	**MS RO+**	**Total (91)**
Wait and see	7	0	0	4	0	0	11
Curettage/surgery	21	2	0	13	0	0	36
LCH protocol	9	9	2	8	6	2	36
Other	0	1	0	2	0	0	3
Lost to FUP or excluded	3	0	0	2	0	0	5

Of those eligible, 12 cases were not treated on LCH protocol as shown in table 6.14. These included one case with MF bone disease, eight with risk of CNS (skull) lesions and three MS low risk patients. Of the nine patients with bone disease, six had had a biopsy, curettage or surgery and one had received 'Other' treatment. The remaining two were 'Wait and see' and in one case the disease regressed spontaneously. Two of the MS cases (bone and DI) were 'Wait and see' and the third received 'Other' treatment.

Table 6.14 Eligible cases not treated on LCH protocol

Treatment	SS bone	SS-MF bone	MS RO-
Wait and see	2		2
Surgery	5	1	
Other	1		1
Total	8	1	3

6.10.3 Reactivation

The follow up questionnaire asked for patient status at their last follow up as described in table 4.9. Any data about reactivation or progression of disease (definitions in section 2.1.5) was provided voluntarily by clinicians as additional information. The questionnaire did not specifically ask about any periods of complete resolution (CR) of disease, nor did any clinician specify any.

Eight children, 1 MS RO+, 5 MS RO- and 2 SS (one skin and one bone) were reported to have had reactivated disease since diagnosis although at the time of follow up two of these cases had no active disease. The sites of reactivation were not stated in half the cases but two children were reported to have disease in new sites. One MS RO- case developed disease of spleen (in addition to skull and ear) and a SS case of scapula bone disease progressed to vertebra.

6.10.4 Permanent consequences

23% of cases (20) were reported to have permanent consequences – eleven males and nine females. There were nine MS cases and 11 SS cases including two MF bone cases as shown in table 6.15. There was no significant difference between those with and without sequelae by age at diagnosis or time from symptoms to diagnosis ($p=0.07$ and $p=0.64$ respectively). Similarly, there were no differences by sex ($p=0.1$) or type of

disease (p=0.5) but there was a difference by type of treatment (p=0.01). There were nine cases on LCH protocol compared with an expected number of 5.9.

Table 6.15 First follow up: cases with permanent consequences by sex and type of disease

Sex	Type of disease				
	SS Bone	SS-MF Bone	SS DI	MS RO-	MS RO+
Male	3	1	2	5	
Female	4	1		3	1

The main permanent consequences were DI and orthopaedic problems with small numbers with various hormone deficiencies, lung, neurological and ophthalmic problems. The frequency of permanent consequences by disease type is shown in table 6.16. Two MS cases developed DI after the original diagnosis and another MS case with DI developed Thyroid Stimulating Hormone (TSH) deficiency. Eight of the nine cases with orthopaedic problems had vertebral collapse.

Table 6.16 First follow up: permanent consequences by type of disease

	Type of disease	
Permanent consequences	**SS**	**MS**
Orthopaedic	9	
Diabetes insipidus (DI)	2	7
Growth hormone deficiency (GHD)		3
Thyroid-stimulating hormone (TSH) deficiency		2
Follicle-stimulating hormone (FSH) deficiency		1
Adrenocorticotropic hormone (ACTH) deficiency		1
Ophthalmic	1	
Neurological		1
Lung		1

Six of the 20 cases had DI at diagnosis (and no other permanent consequences) and therefore did not contribute to the person years at risk (118 years) in the Kaplan-Meier survival analysis. Of the remaining 14 cases with permanent consequences, there were six males and eight females. Overall, sequelae-free survival was estimated to be 42% after 3.3 years (CI: 13%-68%) – figure 6.14. However, at two years after diagnosis which included 11/14 cases it was 73% (CI: 55-85%).

Disease-free survival for different subgroups, based on sex, age group, type of disease, type of treatment and the time period between symptoms and diagnosis, was assessed and the results are shown in figures 6.15 to 6.19. Data for each subgroup were available for all 86 cases except for the time period between symptoms and diagnosis where the date of first symptoms was missing for six (SS bone) cases. P-values are shown and the numbers in each subgroup are given in brackets on each graph. Although there were variations there were no significant differences in any of these subgroups in the probability of surviving without permanent consequences except with type of treatment (p=0.03). As shown in figure 6.19 the probability of having no permanent consequences was 24% in those treated on LCH protocol and 31% in those who received no treatment.

Figure 6.14 Overall probability of having no sequelae at first follow up

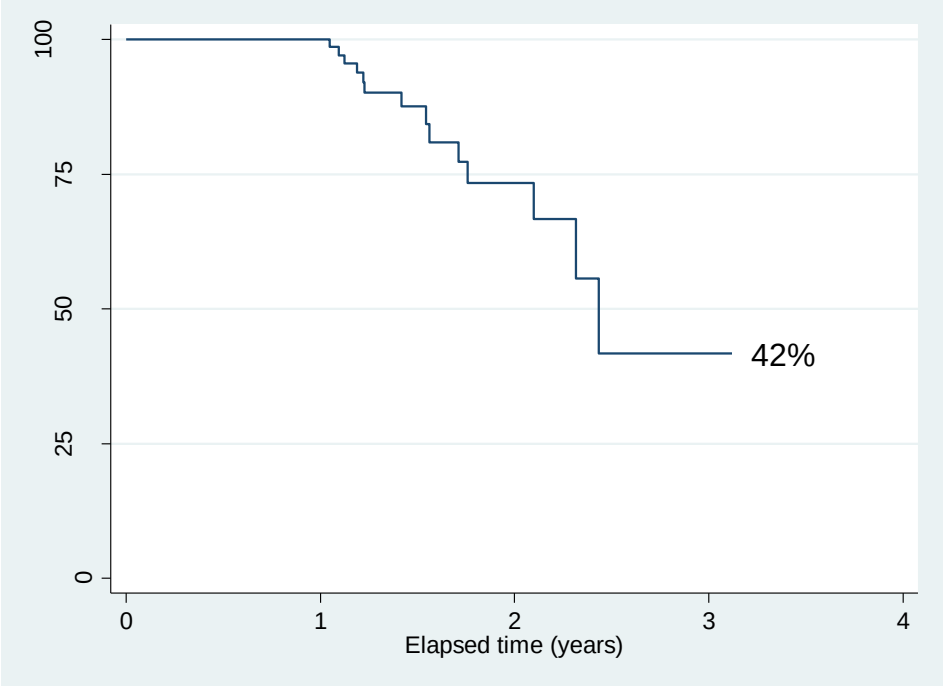


Figure 6.15 Probability of having no sequelae by sex at first follow up

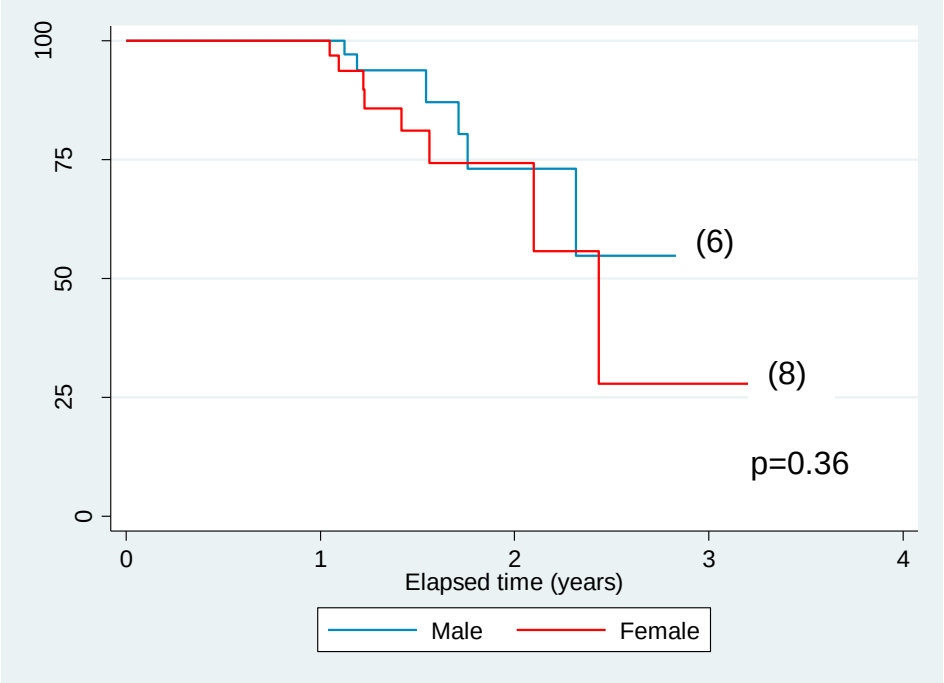
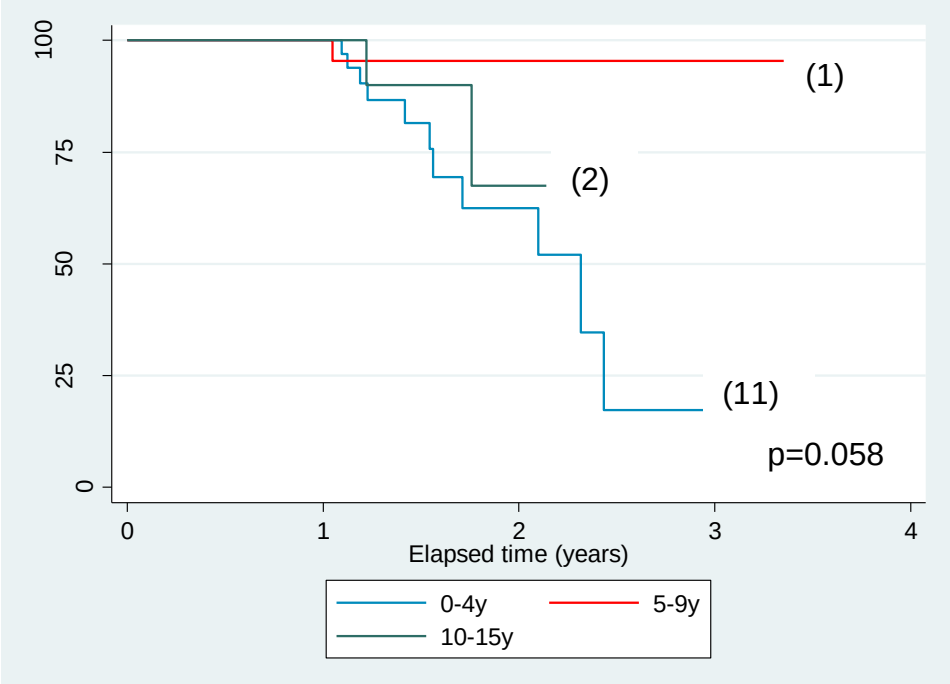


Figure 6.16 Probability of having no sequelae by age group at first follow up



The number of cases in each subgroup is shown in brackets.

Figure 6.17 Probability of having no sequelae by type of disease at first follow up

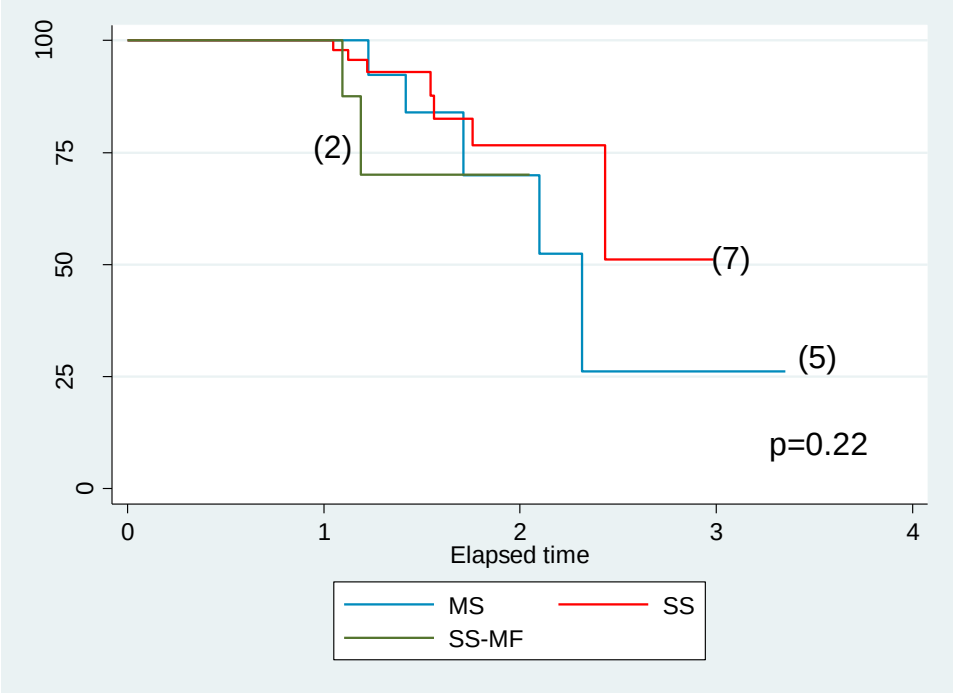
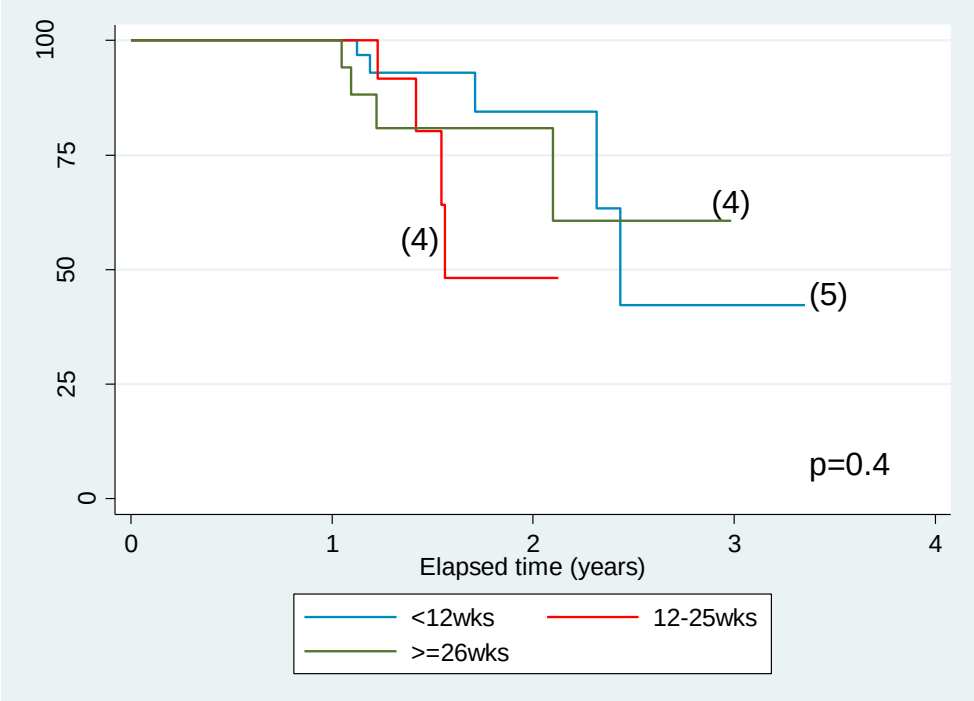
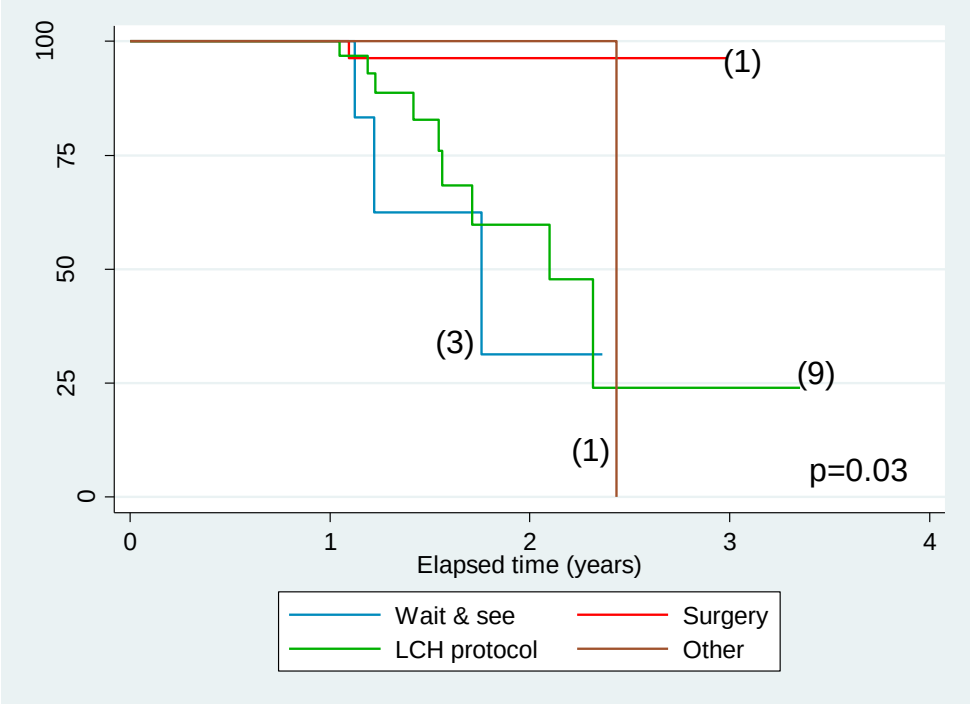


Figure 6.18 Probability of having no sequelae by time from symptoms to diagnosis (weeks) at first follow up



The number of cases in each subgroup is shown in brackets.

Figure 6.19 Probability of having no sequelae by type of treatment at first follow up



The number of cases in each subgroup is shown in brackets.

6.11 Second follow up

All 91 surviving cases were followed up two years after the date of diagnosis. Questionnaire replies were received between 2007 and 2009 and the results were as follows:

- ten cases were lost to follow up.
- one child previously diagnosed with bone disease on the basis of radiological findings had a probable change of diagnosis ("likely diagnosis juvenile axial osteoporosis – probably not LCH").
- two children with SS bone disease who were discharged less than one year from diagnosis were excluded from further analysis.

All those lost to follow up were cases of SS bone disease with the exception of one child with MF bone disease who had moved elsewhere and a MS RO- case for whom no questionnaire was received.

Of the 78 cases assessed, the median number of years from diagnosis was 3.5 years (range 1.0-6.2 years). There were 45 males and 33 females (ratio 1.4:1) which comprised 47 SS, 10 MF bone and 21 MS cases.

6.11.1 Status

Of the 71 cases without active disease, five had been discharged. Only seven cases had active disease. The SS DI cases were reported and classified as having no active disease. The status of cases is shown in table 6.17.

Table 6.17 Cases in second follow up by status and type of disease

Status	MS	SS	SS-MF	Total
No active disease	16	45	10	71
Active disease	1	1	0	2
Active disease on treatment	4	1	0	5
Total	21	47	10	78

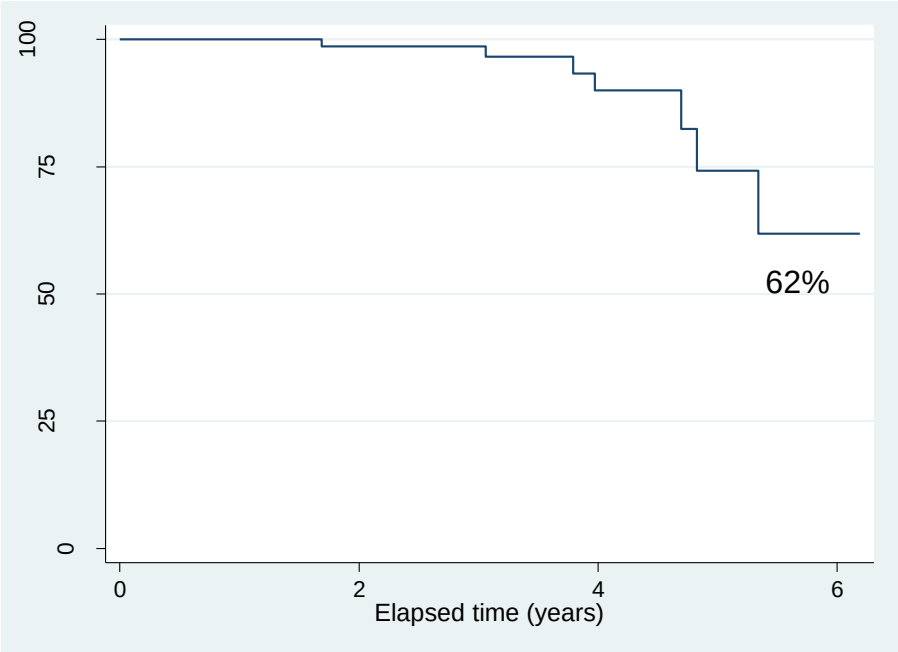
There was no difference in those with or without disease by sex (p=0.12), age at diagnosis (p=0.24) or the time from symptoms to diagnosis (p=0.36) although there were differences by treatment type (p=0.006) and disease type (p=0.03). There were a higher than expected number of MS cases and those treated on LCH protocol or other chemotherapy. In fact, all cases with active disease had received or were receiving treatment on LCH protocol. A description of these cases is shown in table 6.18.

Table 6.18 Cases with active disease at second follow up

Case ID	Sex	Type of disease	Site at diagnosis	Age at diagnosis (years)	Previous LCH protocol	Recent/ current treatment
86	M	SS bone	Orbit	2	Yes	Other
4	M	SS bone	Mandible	10	Yes	Surgery
43	F	MS RO-	Temporal bone, skin	<1	Yes	Other
78	M	MS RO-	Bone (MF), skin	<1	Yes	Other
67	M	MS RO-	Skull, femur, skin	1	Yes	Other
69	M	MS RO-	Ears, nervous system	2	Yes	Other
130	M	MS RO-	Skull, skin, nervous system	14	No	LCH protocol

Kaplan-Meier survival analysis was used to assess active disease-free survival two years after diagnosis. There were a total of 272 person years of follow up. Overall there was a 62% probability of active disease-free survival after 6.2 years (CI: 28%-83%) as shown in figure 6.20. The probability at 5 years (with 6/7 active disease cases) was 74% (CI: 46-89%).

Figure 6.20 Overall probability having no disease at second follow up



Since only seven cases had active disease, subgroup analysis was performed only by sex and type of disease. Neither test had significant results (p values were 0.15 and 0.19 respectively).

6.11.2 Reactivation

Six children (all MS) were reported to have had reactivated disease in the second follow up period although only four had current active disease. Five had reactivation of bony lesions and one had skin lesions. As can be seen from table 6.19, four cases had reactivation of disease in new sites – skin, bone or diabetes insipidus. The first three cases had reported reactivation of bone disease in the previous follow up.

Table 6.19 Sites of original disease and reactivation at second follow up

Case ID	Original site of disease	Site of reactivation	Age at diagnosis (years)	Status
43	Temporal bone, skin	Bone (temporal, petrous)	<1	AD
44	Skin, ears, liver, lung, gut, genital mucosa	Bone, DI	<1	NAD
78	Bone (MF), skin	Bone, DI	<1	AD
65	Skin, thymus	Skull, pelvis	<1	NAD
69	Ears, nervous system	Skin (perianal)	2	AD
130	Bone, skin, nervous system	Bone	14	AD

6.11.3 Permanent consequences

16 cases were reported to have permanent consequences – 11 males and five females. There were 10 MS cases and 6 SS cases. The main sequela was DI (11 cases) with small numbers with various hormone deficiencies, lung, neurological and ophthalmic problems. A list of permanent consequences by disease type is shown in table 6.20. Compared with the previous follow up there were three new cases of DI – in a case with SS disease of the jaw, a MS case with multifocal bone and skin disease, and a MS RO+ case.

Table 6.20 Frequency of permanent consequences by system type at second follow up

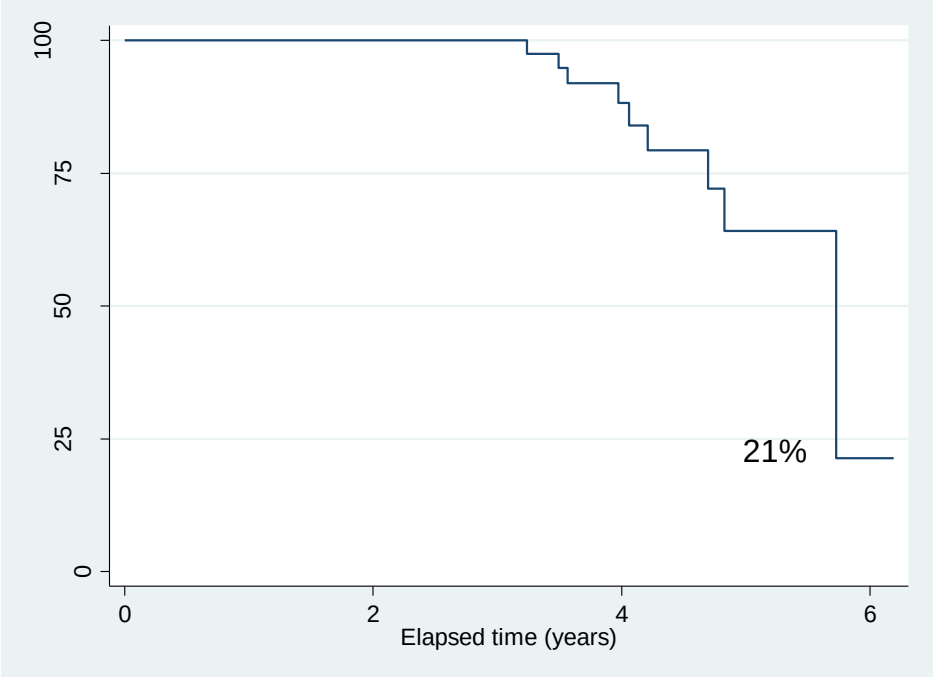
Permanent consequence	Type of disease	
	SS	MS
Diabetes insipidus (DI)	2	9
Growth failure	1	1
Growth hormone deficiency (GHD)	1	4
Thyroid-stimulating hormone (TSH) deficiency		3
Follicle-stimulating hormone (FSH) deficiency	1	1
Adrenocorticotropic hormone (ACTH) deficiency	1	1
Ophthalmic	1	1
Dental		1
Orthopaedic	2	
Neurological		3
Lung		1

Only 11/20 cases with permanent consequences in the previous follow up were reported in the second follow up. The differences were as follows:

- 2 cases were lost to follow up (including one RO- case with DI)
- 1 case with orthopaedic problems changed diagnosis
- 6 cases previously with orthopaedic sequelae were not stated to have permanent consequences
- 5 additional cases had permanent consequences

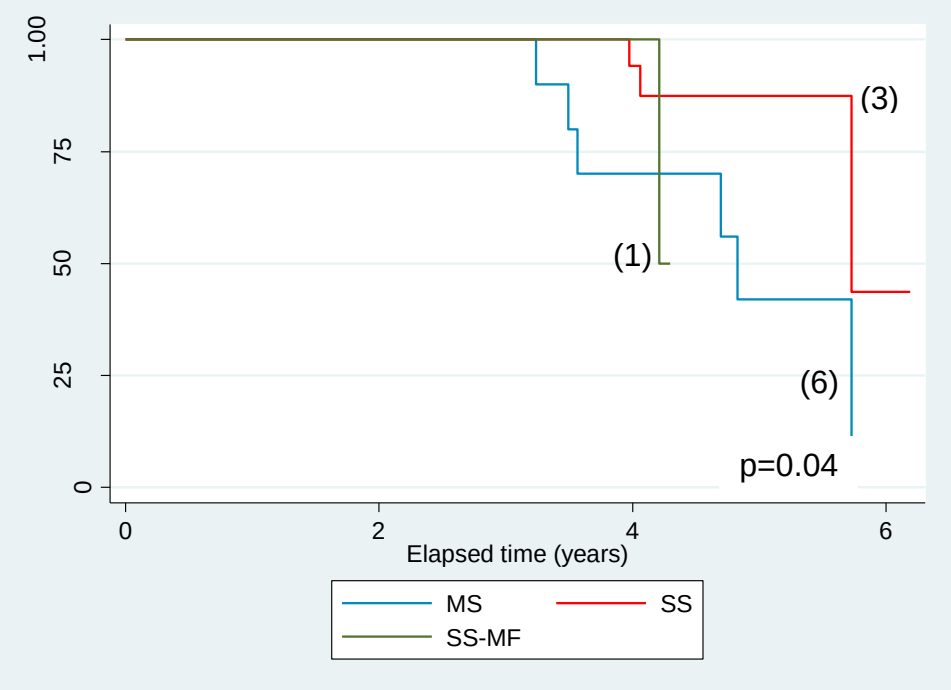
Of the 16 cases with permanent consequences, six had DI at diagnosis and no other sequelae and therefore did not contribute to the person years at risk (249.5 years) in the Kaplan-Meier survival analysis. Overall, sequelae-free survival was estimated to be 21% (CI: 1.2-59%) at 6.2 years follow up as shown in figure 6.21. However, at 5 years with 8/10 cases with permanent consequences, it was 64% (CI: 37-82%).

Figure 6.21 Overall probability of having no sequelae at second follow up



Although the numbers were small, sequelae-free survival between different subgroups – sex, age group, type of disease, type of treatment and the time period between symptoms and diagnosis – was assessed. Data for each subgroup were available for 72 children, except for the time period between symptoms and diagnosis where the date of first symptoms was missing for two (SS bone) cases. The results were not significant for sex or age group (p values 0.66 and 0.29 respectively) but were significant for type of disease (p=0.04), treatment type (p=0.02) and the period from symptoms to diagnosis (p=0.01). Sequelae–free survival curves for the significant results are shown in figures 6.22 to 6.24.

Figure 6.22 Probability of having no sequelae by type of disease at second follow up



The number of cases in each subgroup is shown in brackets.

MS cases had a lower probability (42%) of being sequelae-free compared to the SS cases (87%) at five years from diagnosis (figure 6.22). All ten patients with permanent consequences had been treated on LCH protocol (figure 6.23), the probability being 40% after 5 years.

Cases that had been diagnosed in less than 12 weeks had a higher probability (92%) of being without permanent consequences after five years compared with those diagnosed later – 49% and 29% in those diagnosed between l2-25 weeks and more than 26 weeks respectively (figure 6.24).

Table 6.21 shows all ten cases with permanent consequences that were included in the analysis, by type of disease, sex, the time period between symptoms and diagnosis and treatment. There were four cases with diabetes insipidus. These included one SS bone, one MS RO+ and two MS RO- cases. Six cases with diabetes insipidus at diagnosis and without other sequelae are not shown.

Figure 6.23 Probability of having no sequelae by type of treatment at second follow up

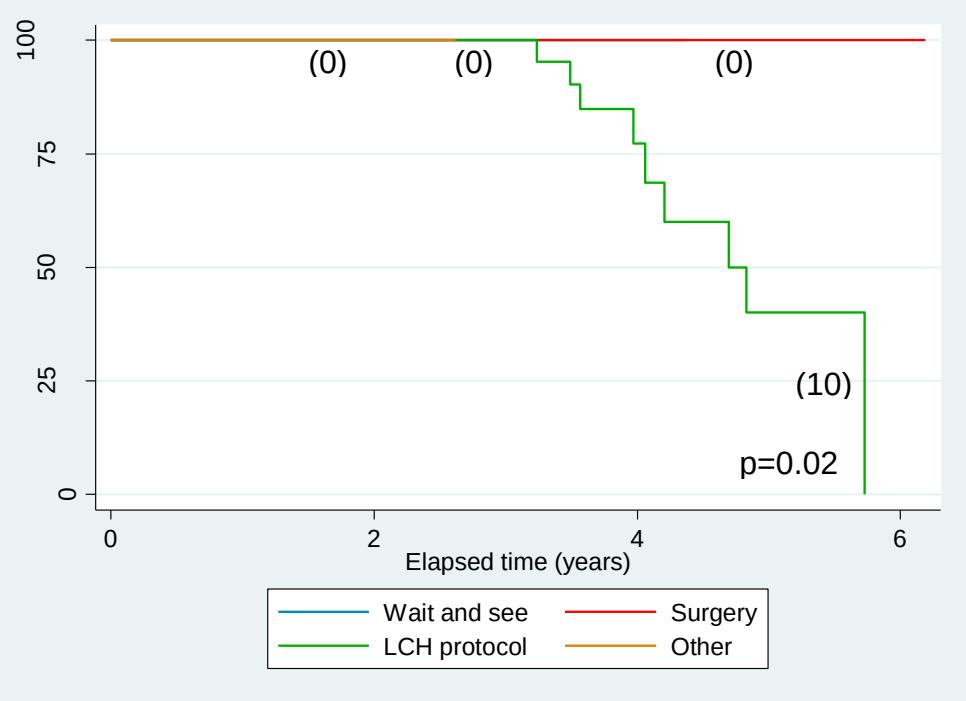
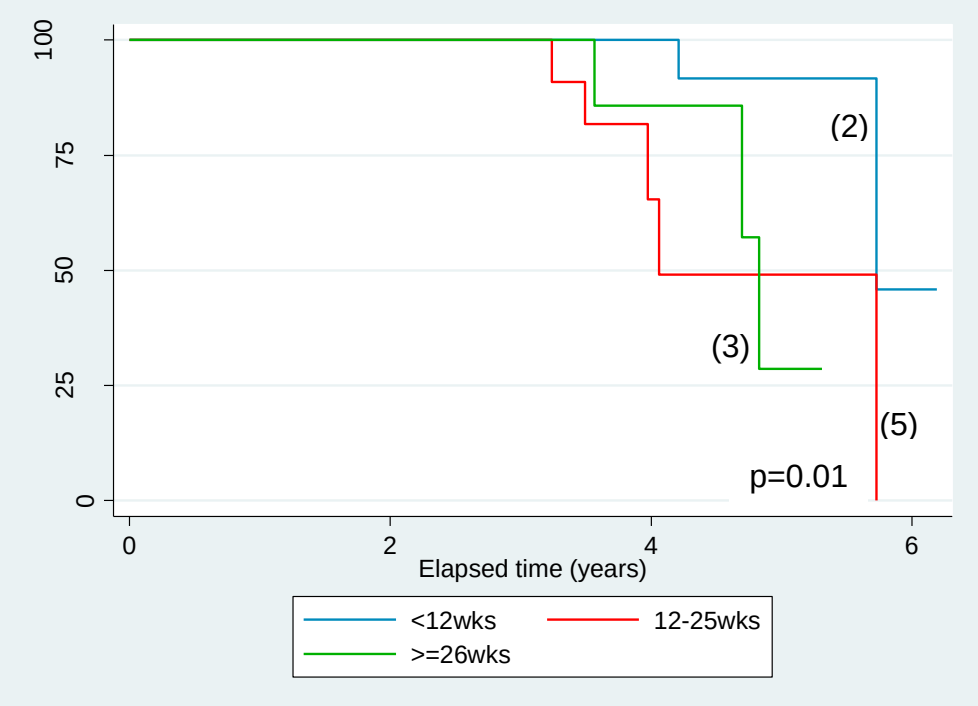


Figure 6.24 Probability of having no sequelae by time from symptoms to diagnosis (weeks) at second follow up



The number of cases in each subgroup is shown in brackets.

Table 6.21 Cases with permanent consequences >2 years from diagnosis included in analysis

Case ID	Type of disease	Sex	Time from symptoms to diagnosis (weeks)	Treatment type
7	SS-MF	M	7	LCH protocol
5	SS B	M	10	LCH protocol
45	MS RO-	M	13	LCH protocol
50	MS RO-	F	13	LCH protocol
23	SS B	F	17	LCH protocol
44	MS RO+	F	21	LCH protocol
4	SS B	M	22	LCH protocol
65	MS RO-	F	29	LCH protocol
69	MS RO-	M	31	LCH protocol
78	MS RO-	M	27	LCH protocol

6.11.4 Co-morbidity/other conditions

In addition to the cancers and co-morbidities listed in sections 6.8.1 and 6.8.2, the following conditions were reported; one case diagnosed at 13 years of age with MF bone disease was reported to have Crohn's disease and was also pregnant; a male diagnosed with lymph disease was being seen by a dermatologist for a congenital hairy compound naevus.

6.12 Mortality

There were three deaths among the study group (described in section 6.9) giving a mortality rate of 3.2%.

The UK and Irish national statistics offices registered 18 deaths over a 10-year period (1996-2005) and this survey identified two further deaths. Combining these data, figure 6.25 shows that 13 boys and 7 girls died. 19 deaths occurred in the UK and one in RoI over the 10-year period. Figure 6.26 shows the number of deaths by age. All were under five years of age.

The age-standardized mortality rate (ASR) was 1.91 per 10 million per year in children aged 0-14 years (CI: 1.905-1.916). For those aged 0-4 years the ASR was 5.25 per 10 million (CI: 5.22-5.27).

Figure 6.25 Number of deaths 1996-2005, by age at death

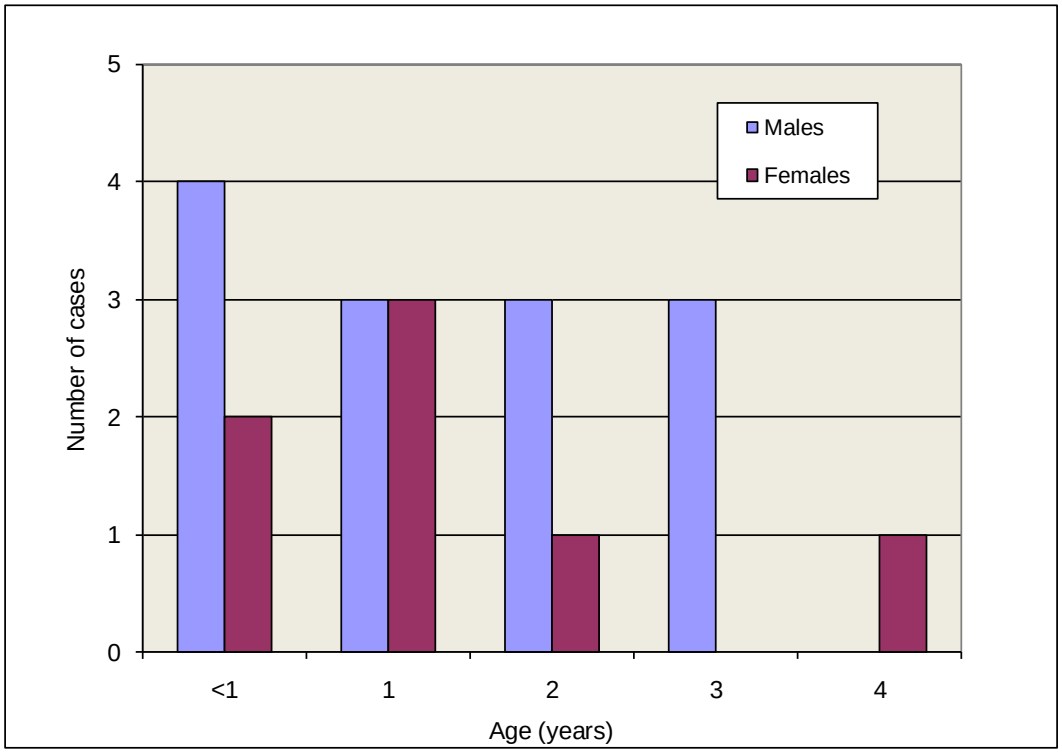
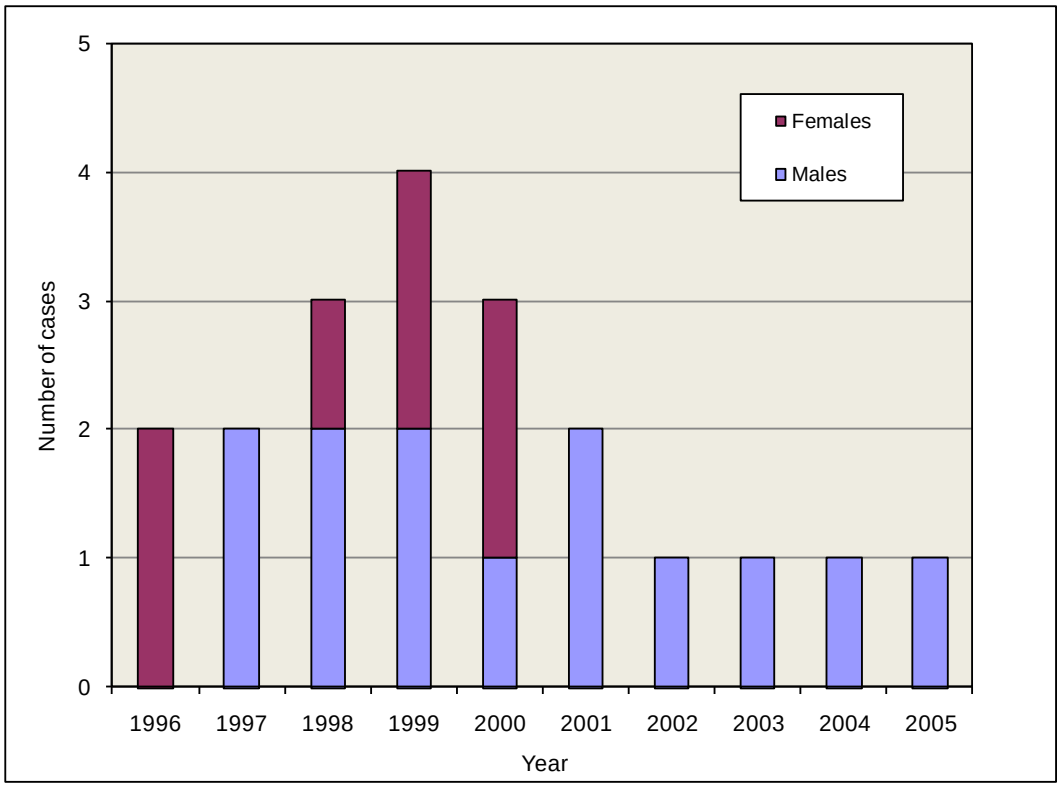


Figure 6.26 Number of deaths with LCH on the death certificate, 1996-2005

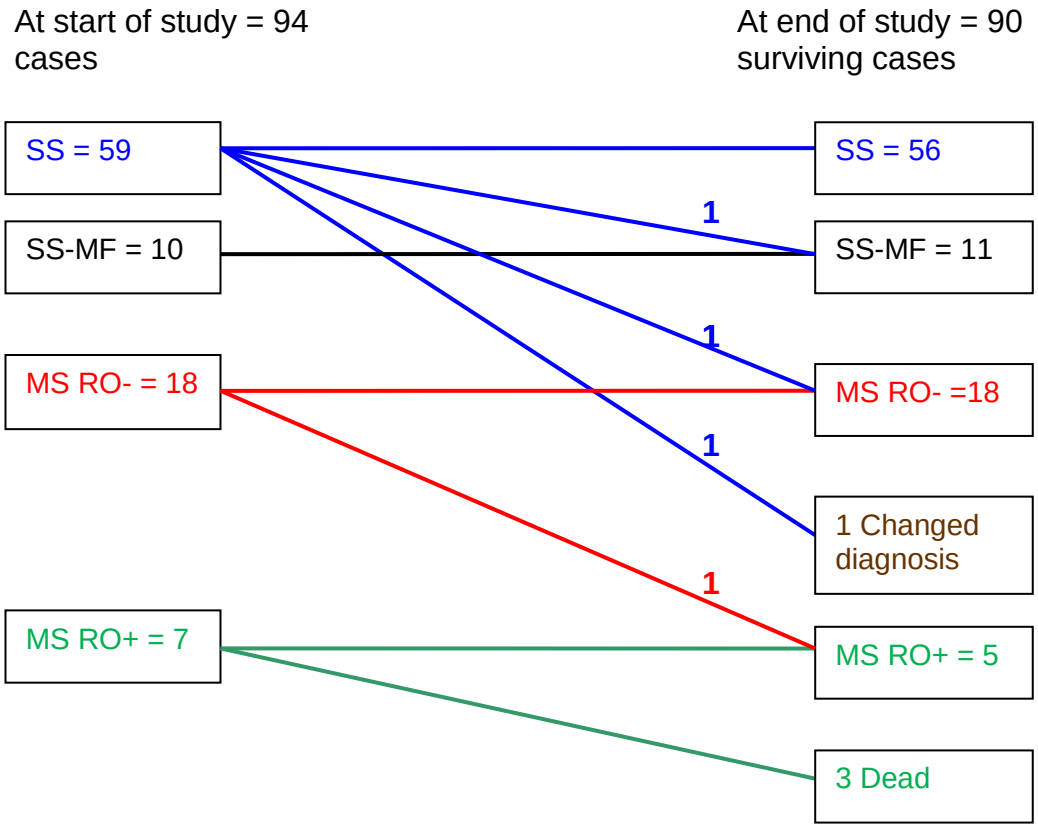


6.13 Summary of cases at end of study

Figure 6.27 is a graphic representation of the outcome of all 94 cases at the end of the study using information received from both follow ups. The figure shows the number of cases by type of disease and progression to other forms, if any, during the interim between diagnosis and the last follow up. For example, looking at the 59 SS cases

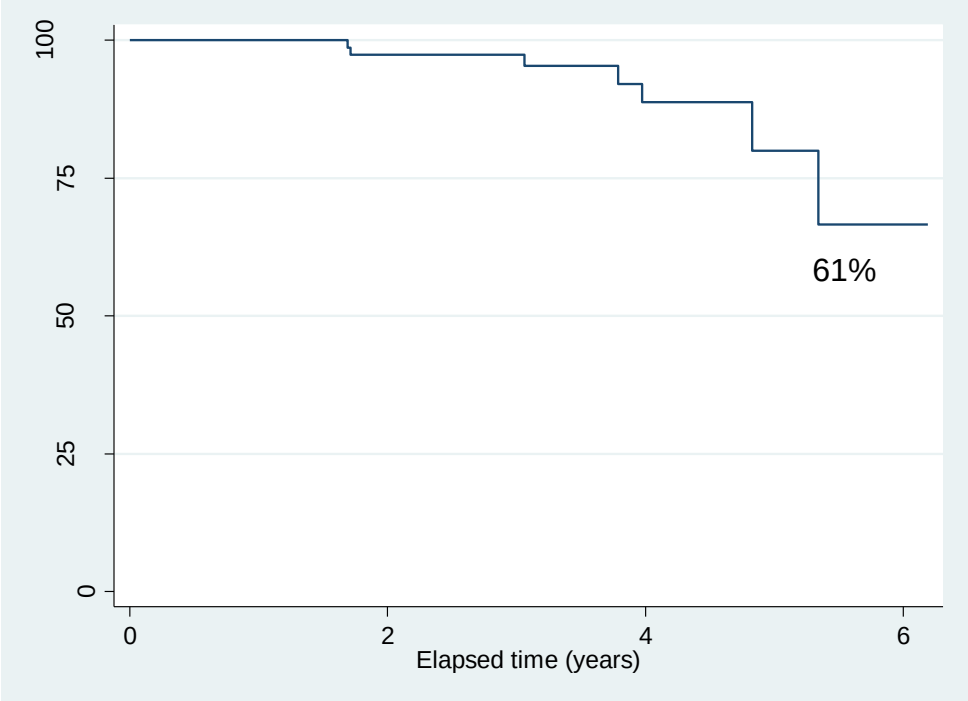
- one case had a changed diagnosis
- one case developed multifocal disease
- one case developed MS disease
- in 56 cases the original diagnosis was unchanged

Figure 6.27 Development of disease from diagnosis to last follow up



Disease-free survival was assessed for all surviving cases using the date of the last known consultation (90/91 cases) from both follow ups and the survival curve is shown in figure 6.28. There were eight cases with active disease; six males and 1 female, as listed in table 6.18, with the addition of another male diagnosed aged 4 years with MS RO- disease who was lost to follow up after 1.7 years. There were 283.6 years person years at risk with a median follow up of 3.1 years (range 0.2-6.2 years). There was 61% probability of being disease free after 6.2 years (CI: 28-82%). The confidence intervals were very wide and the probability was 73% (CI: 45-85%) after five years.

Figure 6.28 Probability of having no disease using data from both follow ups



The main permanent consequence at the last follow up was DI and was found in 13% of cases. Five cases developed DI after the original diagnosis – three with MS RO- disease, one with MS RO+ disease and one with SS bone disease of the jaw.

Overall, at their last follow up

- 96% of cases were alive
- 91% had no active disease
- 8% had been discharged
- 18% had permanent consequences

With the loss of one case (probable changed diagnosis) the age-specific IR was adjusted to 3.7 per million per year aged 0-15 years (CI: 3.0-4.5) and the ASR was 4.08 (CI: 4.07-4.09) per million per year aged 0-14 years.

Chapter 7. Discussion and evaluation

7.1 Summary

The incidence of LCH in children in the UK and Ireland is comparable with other national studies and with regional UK studies. The mortality rate is comparable with the only other rate reported, in France. The study used a well-established prospective method of surveillance with additional sources of ascertainment, the importance of which were demonstrated. The estimate of completeness was 93% which is comparable with other national studies and registries. By including a wide range of clinicians in the survey, 25% more cases were identified than via the CCLG alone (previously the main source of information on LCH cases).

The study fulfilled its aims by describing the presenting features of LCH, referral patterns, and the time taken to diagnose. The spectrum of disease was broadly similar to that reported in previous studies in that approximately two-thirds of cases were of SS bone disease, mainly in older children, and a third of cases were of MS disease, mainly in younger children. 50% of MS cases and 10% of SS cases had active disease or had reported reactivation of disease at one of the follow ups. Those most at risk of active disease were MS cases or those treated on LCH protocol. 18% had permanent consequences at the end of the study, the main sequela being DI. These results are discussed further below.

The study also aimed to give some indication of possible risk factors for the disease. Data collection was limited and since this investigation was conducted over a relatively short period, there were insufficient numbers to draw any firm conclusions on associations with LCH. Given these limitations, an association was found with month of diagnosis – a higher number of cases than expected were diagnosed in spring months. However, no association was found with the month of first symptoms which may better suggest a childhood infectious agent. There was also evidence of a possible association with ethnic origin; the proportion of non-Caucasian children was higher than that in the general population although this may not reflect the age structure of some non-white groups. The results have, however, suggested areas for future study and these are discussed in the concluding chapter.

7.2 Case ascertainment

7.2.1 Response to mailing

On average, 92% of the BPSU report cards were returned by clinicians during the study period compared with an overall response rate of 93% in recent years. This high level of reporting may be a reflection of regular communication with reporting paediatricians, encouraging response. Overall, 53% of clinicians responded to the Newcastle Survey. However, the mailing list had been adjusted after the first mailing (reducing numbers) and the average response for the other three mailings was 58%. In retrospect, the Newcastle survey may have been improved by more frequent mailing, for example, three-monthly rather than six-monthly mailing as this may have enabled clinicians to remember the study and identify cases more easily. However, this was not possible because of limited funding and workload considerations.

Other strategies to maximise response rates to postal questionnaires have been employed as described by Edwards et al in two systematic reviews [181, 221]. Effective methods included the use of short questionnaires and coloured ink, monetary incentives, and questionnaires sent by recorded delivery or first class post. Other strategies which were found to increase response rates were contact prior to the questionnaire being sent, personalised questionnaires, university-originating questionnaires, stamped return envelopes, follow up contact and sending a second copy of the questionnaire – all of which the Newcastle survey employed. Respondents were less likely to return questionnaires requiring sensitive data and indeed, in this study, one or two clinicians queried the lack of patient consent. In addition, the length of the initial questionnaire may have been off-putting. However, although monetary incentives would not have been possible, a shorter more colourful format and the use of first class postage may have elicited a better response.

Time lags in reporting were not considered an impediment to ascertainment since the BPSU continued surveillance for an additional month beyond the end of the study period and the CCLG similarly notified cases for several months after the survey ended.

Although every effort was made to follow up reports of cases 53 questionnaires (14%) were not returned. 18 of these corresponded to cases (both eligible and ineligible) notified by a clinician at the same hospital at approximately the same time. Clinicians were reminded to return questionnaires but could not remember the name of the patient

diagnosed and frequently asked for identifying information. In a recent evaluation of the BPSU system, 68% of paediatricians reported no difficulties in identifying cases but other reasons given for not confirming cases included problems with finding notes and time consumption with no obvious immediate benefit [222]. The anonymity of the BPSU system, while effective in avoiding bias and delay associated with obtaining patient consent, does have limitations.

7.2.2 Reporting rates and patterns

As might be expected, the highest rate of reporting was by the CCLG (80%) with the BPSU and Newcastle surveys identifying 73% and 62% of cases respectively. Cases treated without chemotherapy may not be registered with CCLG and cases of uncomplicated bone disease in older children may be treated without paediatric input. The study was therefore designed to use three complementary sources of ascertainment. The specialties of respondents to the Newcastle survey were proportional to the specialties of those on the mailing list with the majority being pathologists. Overall, the clinicians who confirmed cases were mainly oncologists and paediatricians (60%) with 15% identified by pathologists and 13% by orthopaedic surgeons. In general, this reflected the proportion of cases reported by, and the limitations and advantages of each source.

The percentage of cases ascertained by the CCLG was lower than their estimate of registering 90-95% cancers and LCH cases in the UK [173]. However, the majority of cases missed by CCLG (and BPSU) were of unifocal bone disease requiring little or no treatment suggesting that cases were appropriately collected. During the study period LCH III trials began with chemotherapy protocols for MS, MF or special site UF disease which most likely contributed to the appropriate registration of cases by CCLG. The BPSU survey uniquely identified two infants who had died with MS RO+ disease, cases which would not have been reported routinely to CCLG, and neither of which were among those registered by ONS. Thirty-six cases were not identified by the Newcastle survey which extended outside general paediatrics. However, by including pathologists and orthopaedic surgeons in particular, the survey was successful in uniquely identifying 10 UF bone cases although this may indicate under-reporting in this area. The study may have further benefited from cross-checking with the British Society for Children's Orthopaedic Surgery (section 3.5), the Scottish Bone Tumour

Registry and other orthopaedic groups although bone cases which regress spontaneously may not be recorded by any group.

Only one 15 year old was identified and no older teenagers. Although the survey asked for children "of any age" to be reported, it is possible that some in their late teens may have been diagnosed and treated at adult centres. This group of older children may have been covered to some extent, by the inclusion of non-paediatricians on the Newcastle mailing list although targeting of specific non-paediatric societies such as the British Association of Dermatologists and dental associations would have widened the net. However, in the North of England no cases of LCH were reported in 15-19 year olds between 1968-1995 [25]. Referral patterns across the UK are very variable and at many CCLG treatment centres relatively few older children are registered [21]. The Paediatric Oncology Unit in Bristol reported that 10% of its registrations (cancers and LCH) were more than 15 years old which was much higher than at most other CCLG centres except Leeds, Manchester and London. The introduction of Teenage/Young Adult (TYA) centres, recommended by NICE in 2005, may have improved both referral pathways and registration of older children since then [223].

Although LCH has well-defined diagnostic criteria (section 1.3) cases diagnosed without a biopsy may be less certain. In this study 13% had been diagnosed by typical radiological appearance and for one case the basis of diagnosis was not stated. However, there had been some initial over-reporting. The survey asked for reports of all suspected as well as confirmed cases and during the surveillance period almost 100 cases were identified. However, over the following months, several of these diagnoses changed. Indeed, it was only at the end of the second follow up period that one case was thought 'likely to be juvenile osteoporosis, probably not LCH'.

Incidentally, as many adults as children were reported during the survey – via the Newcastle survey and questionnaire returns (section 5.2) – a finding similar to the LCH-Belgian Survey Registry [44]. This leads one to suspect that a well-designed study to identify adults with LCH may confirm an incidence rate much higher than previously thought [125]. Interestingly, the Northeast region reported an incidence rate of 0.6 per million per year in 20-24 year olds which may be associated with smoking patterns in this age group [25]. The aetiology of pulmonary LCH is associated with smoking in adults and is most frequent in 20-40 year olds (sections 2.1.2 and 2.4) [55, 224].

7.2.3 Capture-recapture estimates of completeness

38% of cases were identified by each of the sources. As expected, there was a high degree of overlap in cases identified by the BPSU and CCLG (25%) and a smaller overlap in cases identified by each of these with the Newcastle survey (12%). However, there may still have been some under-ascertainment. In a recent BPSU report, the main reasons given for not reporting cases, apart from not seeing a case, were that paediatricians (12%) thought or expected that a colleague had reported it or had forgotten the details when the 'orange card' arrived [222].

C-RA has been advocated as a useful method of quantifying undercounting in surveillance studies although others have questioned its applicability given the inherent uncertainties involved [45, 225-227]. In any case, results should be viewed with caution, since bias may occur if any of the requirements of C-RA are invalid (section 4.1.1) [187]. As discussed by Hook and Regal, in epidemiological studies, it is difficult to guarantee that all assumptions have been met. In this study, as well as paediatricians notifying both the BPSU and CCLG, discussion or collusion between colleagues may have taken place affecting ascertainment by all the sources. In addition, the BPSU survey (paediatricians) and Newcastle survey (non-paediatricians) might have been considered not 'to be fishing in the same pool'. However, it was assumed that cases would have the same chance of being identified by pathologists as by the clinicians who treated them. The main problem with C-RA is that there is an assumption that the "unobserved individuals will behave as the observed individuals" and patients who are not recorded on any list may be unusual [227, 228]. In this study, there is tendency to 'capture' more severe cases.

With these caveats in mind, ascertainment by the Newcastle and BPSU surveys was estimated by C-RA at 86% (14 missing cases) although an additional six cases were identified by the CCLG. The use of multiple sources and models limits the risk of bias [225, 227]. In this study, by using the three-source model to incorporate the CCLG cases and account for the positive dependence (large overlap) between the BPSU and CCLG, the estimate was adjusted. The total number of expected cases was almost the same (101 versus 102 cases) thus confirming the plausibility of the model chosen. The completeness of ascertainment increased to 93% using all three sources.

Few incidence studies have reported the completeness of ascertainment and only one used C-RA. However, our estimate is comparable with ascertainment in a recent French study (97%) and European and UK regional cancer registries that have reported LCH incidence rates (90-95%) [2, 3, 20, 29]. However, although cancer registries use several sources of ascertainment, given the heterogeneity of LCH, it is likely that ascertainment of LCH cases by them is less complete than for cancers. It has been advocated that any epidemiological study or registry collecting data to report incidence rates of disease should record the source of each case [187, 225]. As well as allowing monitoring of each source, an estimate of the completeness of ascertainment would allow more accurate estimates of incidence rates. Given the estimated of completeness of ascertainment of our survey, a further seven cases would have increased the age-specific IR marginally to 4.02 per million per year age 0-15 years (CI: 3.27-4.89).

7.3 Strengths and weaknesses of the survey methods

The study is the first national study to use a prospective method of identifying LCH cases. It relied on clinicians notifying new cases as opposed to identifying cases previously diagnosed. Advantages of this method are that new or suspected cases are likely to be more easily recalled, records may be more readily available and accurate, and cases are unlikely to be missed due to changes in disease classification. In these respects a prospective survey is likely to improve ascertainment. In addition, a prospective study may capture specific variables whereas historical records, designed for other purposes, may not have recorded them. However, new cases of a rare disease take a very long time to accumulate. Retrospective studies may be less expensive to conduct and quicker but may be subject to under-counting unless several sources of ascertainment are used. Conversely, over-counting may be a disadvantage in prospective studies, unless, as in this study, sufficient time passes to allow eligibility to be confirmed. The survey was also conducted over a relatively short period. A longer survey combined with retrospective data collection may have identified cases taking a long time to diagnose.

Other artefacts in case ascertainment may bias results; selection bias may be introduced if a clinician decided not to respond to the survey, could not remember a patient or was unable to find patient notes. Given that a number of questionnaires were not returned for

at least one of these reasons, under-ascertainment, also suggested by C-RA, is likely to have occurred.

The number of cases identified in this study exceeded those identified by the CCLG in previous years (averages of 47 and 37 per year respectively). The combination of the three sources used covered the spectrum of disease: more severe cases requiring treatment were identified by CCLG, whereas those seen by paediatricians ranged from cases found incidentally to congenital fatalities. The Newcastle survey was particularly effective in identifying cases referred to orthopaedics although it may have been improved by cross-checking cases with the British Society for Children's Orthopaedic Surgery and the Scottish Bone Tumour Registry. The Newcastle mailing list included adult specialists but did not target specific non-paediatric societies. By including members of such societies, older children referred to adult services may have been identified. Response rates may also have been improved by increasing the frequency of mailing and employing other tactics to encourage replies. Although each surveillance method may have missed recognised cases and mild undiagnosed cases, these observations demonstrate the importance of multiple sources to maximize the completeness of ascertainment.

7.4 Comparison of IR with other studies

While accepting that there was probably a degree of under-ascertainment, the age-standardized incidence (4.1 per million per year aged 0-14 years) is comparable with other national studies in France and Denmark (5.0 and 5.4) and reports from the German and Swiss Cancer registries (6.0 and 4.3). The variation may reflect different methods of ascertainment or the small number of cases.

The biggest differences in rates are likely to be due to differences in methods of ascertainment. The French study, estimated at 97% complete, used two sources of ascertainment while the Danish study used various complementary sources. The importance of multiple sources has been discussed; those studies using a single source generally reported lower rates than those using several sources (section 2.3.1) [119, 120]. All studies were retrospective except for the LCH-Belgian Survey, which reported an IR of 8.3 per million per year (aged <20 years) based on both retrospective and prospective data collection. Interestingly, this rate is among the highest of those

reported. It is also, one of the most recently reported. Differences in IRs may also be due to the time period in which cases were diagnosed. Improved diagnostic techniques, changes in the classification of disease and recording of cases may have an effect on identification of cases as discussed by Alston et al in their study over a 40-year period [2]. Another explanation is that incidence may increase over time. However, none was reported by Alston et al; the LCH-Belgian Survey reported stable incidence over six years and the earliest incidence rate, reported in Denmark for 1975-1989, is comparable with more recent IRs [1, 2, 44].

Incidence declined with age from 9.9 in infants to 1.8 per million per year in children aged 10-14 years. These rates were similar to those in the Northeast and Northwest of England where the IRs for those aged less than one year were 9.0 and 8.0 per million per year and 4.6 and 3.2 for those aged 1-4 years respectively. However our rates for older age groups were higher suggesting better ascertainment of bone disease in these children. The downward trend has been reported in other studies although national rates in infants in France and Germany were much higher than in the UK (15.3 and 23 per million per year respectively – table 2.7). A possibility for this variation may be due to differences in referral patterns or more aggressive diagnosis in young children. Comparisons of diagnostic times are discussed further below (section 7.5.1).

Overall, the incidence in children with SS disease was twice as high as those with MS disease (2.9 versus 1.1 per million per year) which is comparable with recent French and Swedish studies [3, 28]. However, the reverse was the case in infants (3.3 SS versus 6.6 MS cases per million per year). This differs from the French study in which the rates of disease in infants were 8.2, 2.4 and 4.7 for UF, MF and MS RO+ disease respectively. The high rate of SS disease in infants in their study was due to a large number of UF skin cases [3]. The spectrum of disease is discussed further below.

Our incidence rate for those aged 0-14 years is higher than the 2.5 per million per year (42 cases from 1968-1995), the 2.6 per million per year (101 cases from 1954-1998) and the 3.0 per million per year (13 cases from 1980-1984) reported by children's cancer registries in the Northeast, Northwest and West Midlands of England [2, 25, 33]. ASRs for these regions were 3.7, 5.0 and 4.2 per million per year respectively, which taken with the overall rate may suggest a degree of under-reporting or under-diagnosis in the previous reports. The age-specific rate for the Southwest region, 3.2 per million per

year, was comparable with a rate of 3.4 per million per year, calculated from a recent report (16 cases from 2002-2006 aged 0-15 years). No significant difference in regional incidence rates was found; there were too few cases and too little data to indicate any further geographic analyses.

7.5 Comparisons of spectrum of disease

7.5.1 Symptoms and presentation

Patients presented mainly to a GP (80%), the most common symptoms being pain and swellings, which reflect the number of cases with bone disease. Similarly in France, in 77% of cases, the initial presentation involved bone [3]. The low frequency of rare diseases may result in delay in recognition and diagnosis and thus possibly increase the risk of complications and poor outcome. However, diagnostic delay is difficult to define since there may be variations in both patient delay and referral delay. As might be expected, there was wide variation in the time from symptoms to diagnosis although there was a no significant difference between any subgroup. A significant difference between unisystem and MS groups was found in a study in Ireland but further details were not reported [115]. The shortest median time of 9.2 weeks (range 3.1-26.7) was for patients with RO+ disease. The longest median interval, 28 weeks (range 6.7-37) was reported for the six children with "other" disease (two each of SS lymph node, skin and diabetes insipidus). In a US study, the mean age at diagnosis of neonates with skin lesions was 14 weeks [72]. These times are longer than those reported in France; the median time between symptoms and diagnosis was seven weeks for MF or MS disease, and 11 and 17 weeks respectively for cases of skin and endocrine disease [88]. The time from symptoms to diagnosis was even shorter in Stockholm, the median time being one month [28]. Stein et al reported some misdiagnoses in their US study but differences in health systems may account for the shorter times to diagnosis in some European countries since infants and young children may present to paediatricians rather than GPs.

7.5.2 Spectrum of disease

The proportion of those with SS disease was 73% which is a little higher than the 69% reported in Stockholm, 67% in Denmark and 60% in France [1, 3, 28]. In common with other studies, the most frequent site of disease at diagnosis was bone (83%) [3, 28, 58, 64]. The proportion of those with MF bone disease (16%) was similar to previous

reports (range 15-30%) as was the proportion of MS cases with bone involvement (60%) [3, 59]). Of those with SS bone disease, skull was the most common site (25%). However, this was lower than that reported in Stockholm (55%) and by a multi-institutional European study of 178 cases of SS disease (40%) [28, 58]. 18% of cases had skin disease at diagnosis compared with 11% in the European study, 12% in Japan and 34% in Stockholm [28, 58, 64]. The median age at diagnosis of all those with skin involvement was 0.8 years, with only three children older than one year. Although there were only two cases of SS skin disease, it was present in all seven MS RO+ cases and in over half the MS RO- cases. In common with the findings of other studies, skin disease is found predominantly among young children. In France, 78% of all children under one year of age had skin disease and in Japan, the median age at diagnosis was six months [3, 64].

In contrast with our study, 56% of cases in the Northwest of England were MS, the frequency of bone and skin disease being 67% and 37% respectively [2]. The differences may reflect the differences in ascertainment of older children (described above) and consequently the number of cases of SS bone disease.

Overall, the median age at diagnosis was 5.5 years which is higher than several previous reports where the medians were between 2-4.8 years although comparable with the Swiss Registry (5.8 years) [1-3, 28, 29, 64]. Again, this may be explained by the higher proportion of older children with SS bone disease in our study (median age 6.7 years).

The sex ratio was 1.5:1 which is similar to other national reports (range 1.2:1-2.2:1). As in France, male predominance was not observed in those under one year of age (1.1:1). The sex ratio in this study was highest (2.7:1) in the 10-14 years age group which had a high proportion of bone cases (87%).

7.6 Possible associations with LCH

7.6.1 Seasonality

Infectious agents vary themselves by season. If they are involved in the aetiology of childhood LCH then seasonal variation in birth dates or dates of onset of the disease may be apparent. An association with date of birth may suggest a prenatal infectious agent; an agent acting during childhood with a short incubation period from infection to

clinical disease may be more apparent if there is an association with the onset of symptoms (or date of diagnosis as a proxy for the onset of first symptoms). Seasonality may also be apparent if diagnosis occurs more often at some times of the year than others.

Although there have been seasonality studies of leukaemias and other neoplasms (with conflicting results) [209, 212, 229] there have been very few in relation to LCH. A study in Stockholm reported more cases diagnosed during the autumn and winter months (22/29) with a median time between onset of symptoms and diagnosis of only one month suggesting that an infectious agent prevalent in the autumn or another environmental factor may be implicated [28]. Other studies have reported a higher incidence in wet regions or during periods of high rainfall [119, 153]. Seasonality may be more pronounced within types of LCH or within particular age-groups. Although no studies of such subgroups have been conducted, Stalemark et al noted that all MS cases in their Stockholm study group and 3/5 SS patients who later developed MS disease were diagnosed in the winter months. In this study, the only association found was with the month of diagnosis with a peak in spring; a higher number of cases than expected were diagnosed from March to May ($p=0.04$). However, the test used in this analysis (Edwards test) is known to be unreliable for small and medium samples and the result should be treated with caution. In addition, the month of diagnosis is a poor proxy for a childhood infection since even small variations in the lag period between first symptoms and diagnosis could make a difference to the analyses. In this study, symptoms may have developed several months before diagnosis given that the median time from symptoms to diagnosis was 11.5 weeks. The result appears anomalous since no association was found with the month of first symptoms (which more plausibly suggests a childhood infectious agent) although fewer dates of first symptoms were available for the analysis. Seasonal patterns in diagnosis can often be attributed to holiday patterns with more patients being seen before or after a major holiday period, which in this case may have been the Easter holidays. The finding of an association with month of diagnosis is therefore tenous and likely to be due either to chance or a statistical artifact.

A recent seasonality study of cancers and LCH in Northern England found no seasonality in the month of birth or month of diagnosis of 71 LCH cases (unpublished

data) between 1968-2005 and no seasonal associations were reported in the Northwest of England over four decades [2, 230].

7.6.2 Ethnicity

While the majority of LCH studies have described white children with LCH, this may be due to a bias in reporting. The proportion of non-Caucasian children was 14% which was similar to that reported by McClelland et al (13%) in a study at Great Ormond Street Hospital. Compared with the 7.9% of ethnic minorities in the whole population, the proportion of mixed or other ethnicity children was significantly different from the general population (p=0.027). However, ethnicity was not reported in six cases and although the proportion of ethnic minorities as a whole is reported to be 7.9%, it should be noted that some non-white groups in the UK and Ireland have a younger age structure than white groups, especially those of mixed ethnicity (9/13 cases in this study) [231, 232]. This result does, however, provide evidence of a possible association with ethnic origin which might be investigated in a larger study. The percentage of non-white Caucasians in our study is lower than the 27% in Stockholm County although the latter may not have been representative of Sweden as a whole.

7.6.3 Birth and familial factors

Gestational ages and birth weights were not significantly different from those in the general population (p=0.13 and p=0.26 respectively) although the proportions of pre-term and lower birth weight children in the cohort were slightly higher. There were no differences in birth weights or gestational ages of MS or SS cases. Birth weight data were missing for a third of cases but the findings are in keeping with Carstensen and Ornvold's study and two large US case control studies which investigated a large number of factors surrounding pregnancy and birth [1, 141, 142]. Unlike the study in the Northwest region which reported no congenital cases of LCH, there were four (4%) in this study [2]. All had had prominent symptoms from birth although the median time to diagnosis was 8 weeks and one case was only diagnosed post mortem. This is higher than the 2% of cases reported by the Austrian/German/Swiss/Netherlands LCH Study Group and the 5/258 cases in France [3, 54]. However, these studies only included cases diagnosed within four weeks of birth. It was thought that the incidence of neonatal LCH was underestimated since there is evidence that although the condition is present at birth, as in this study, it is not diagnosed until later [54]. Minkov et al also reported that the rate of spontaneous regression in neonates with SS skin disease was 56% (5/9

cases) which may represent a group which are generally under-reported and under-diagnosed.

Both monozygotic and dizygotic twins have been reported to be concordant for LCH. Three children were reported to be twins although there was no information about their siblings. Prior to this study commencing, the Childhood Cancer Research Group in Oxford noted that there were three sibling pairs on their registry. However, the data were old (1964-1972) and it was thought likely that they were actually cases of HLH [233]. Two children were reportedly born after IVF treatment which is similar to the proportion of artificial reproductive technology (ART) births in the UK population (1.3%). However, the study questionnaire was not designed specifically to capture information on either siblings or IVF (or other forms of ART births) and the cases reported were volunteered. No other epidemiological LCH studies have included siblings and, given the conflicting findings of an association with ART by Kallen et al, further studies with larger cohorts may be warranted [160, 161].

In the two US publications on risk factors, LCH was (inconsistently) associated with maternal urinary tract infections, parental solvent exposure, feeding problems and medications during infancy, a family history of thyroid disease and infections in the postnatal period [141, 142]. However, only one mother in this study had a reported thyroid condition and only single cases of infections or other conditions were reported. Interestingly, one mother had Darier's disease, a genetic skin disorder, which has been included in the differential diagnosis of LCH.

7.6.4 Cancer and co-morbidities

Congenital anomalies have been associated with an increased risk of both LCH and cancer [158, 234]. In a study of 39 cases over three decades by Shiels et al, 18% of those with LCH had major congenital anomalies compared to 3% and 8% in control groups. These cases were also more likely to have MS disease. In contrast, only two cases had a congenital disorder – one with partial Trisomy 3 had MF bone disease and a child with congenital LCH (RO+) who died in infancy had multiple intestinal stenoses. Although there have been cases reports of gastrointestinal LCH, it is rare and there has only been one case of intestinal atresia previously published [235]. Few other co-morbidities were reported (section 6.8.2).

One child had a related histiocytic disease, juvenile xanthogranuloma, and two children had medulloblastoma, one of which was diagnosed before LCH. The LCH-Malignancy Registry has recorded over 90 cases of malignancy and LCH, most frequently solid tumours which tended to occur after the diagnosis of LCH (in 62% of cases) [236]. In 13/20 cases, tumours had arisen in the radiotherapy field given to treat LCH. However, radiotherapy is no longer used to treat LCH patients and further details of the medulloblastoma cases in this study are unknown. The reported association of LCH with both congenital anomalies and cancers may suggest a common genetic predisposition.

A female, diagnosed aged 13 years with MF bone disease, was reported to have developed Crohn's disease. There has been one report of an adult case with both diseases [237] although Crohn's disease, a chronic inflammatory disease of the intestine, has been reported with paediatric cases of HLH, rheumatoid arthritis and other auto-immune inflammatory diseases [238, 239]. Given the evidence of over-production of inflammatory cytokines in LCH [133], this may be indicative of some subtle but mutual abnormality of the immune system.

7.7 Follow up

7.7.1 Treatment and reactivation

The study found that 40% of cases had been treated on LCH protocol, 40% had had a biopsy, curettage or surgery, 12% received no treatment and 5% had 'other' treatment. Similarly, in France (2000-2004), 30% were enrolled on a clinical trial and in Stockholm (1992-2001) 45% had systemic treatment. However, 43% of French and 31% of Swedish cases were 'wait and see' [3, 28]. The difference between studies may be due simply to the way in which treatments had been categorized; in this study, the surgery group included cases that had had a biopsy only and no other treatment. All those with active disease at the end of follow up were cases that had been diagnosed 'at risk of reactivation' and consequently were receiving or had received treatment on LCH protocol.

At the end of the first year of follow up (median 1.3 years from diagnosis) no deaths had occurred and 87% cases had no active disease. Few cases (eleven) had active disease (7 MS and 4 SS bone); compared with those without disease, there were significant

differences by disease type (p=0.01) and treatment with a higher than expected number of MS cases and those treated on LCH protocol. The probability of disease-free survival was 68% in SS cases, 55% in MS cases and 100% in MF bone cases (p=0.03). This differs from event-free survival in a study by Jubran et al which was 89% for SS bone, 24% for MS and 58% for MF bone cases with a longer follow up time (median of 5.5.years) [94]. In the present study, there was a borderline difference in disease-free survival by time from the first symptoms to diagnosis (p=0.06); those diagnosed between 12 and 25 weeks had a lower probability of being disease-free than those diagnosed more quickly suggesting that delay in diagnosis gives a poorer prognosis. However, the prognosis improved in those whose took longer than 26 weeks to diagnose. All except one of the cases diagnosed between 12-25 weeks were MS cases, including one with RO+ disease, although there was no pattern in the sites of disease involved. More prompt treatment in those diagnosed early and less severe disease in those who took longer to diagnose may account for the better prognosis in these cases. However, dates of first symptoms were missing in some cases and the finding may be of interest to explore in a larger study.

Comparisons of disease-free survival between the two follow ups are difficult to make since there were differences in both the number and the composition of cases assessed (as described in section 6.11). At the end of the second follow up (median 3.5 years from diagnosis) 91% cases had no active disease. No significant differences were found between those with and without active disease except by type of disease and treatment type. The most severe cases with active disease at follow up had all received or were receiving treatment on LCH protocol. This is to be expected since these cases generally have the poorest outcome regardless of treatment. Some patients do not respond to treatment and the aim of the latest protocol (LCH IV) is to reduce reactivation and progression of disease, particularly CNS disease, while continuing to improve survival.

In each follow up, the number of cases with active disease was very small and the addition of one or two cases can make a large difference to disease-free survival estimates. The overall probability of disease-free survival combining data from both follow ups was 61% (median 3.1 years, range 0.2-6.2 years); there were only eight cases with active disease and the confidence intervals were very wide. (CI: 29%-82%). In a study by Willis et al, event free survival was 30% 15 years after diagnosis, (estimated at

50% at 3 years for comparison with this study) and it did not reach a plateau until 16 years after diagnosis [101].

Reactivation is not directly comparable with other reports since in this study only a snapshot of the patient's disease status was obtained at two time-points after diagnosis. A short-coming of the study is that details of when reactivation or progression occurred were not obtained and it is not known whether there were any periods of complete disease resolution in those with active disease at diagnosis. Clinicians reported reactivation in the original site of disease or, in some cases, progression of the disease to additional sites in space provided on the follow up questionnaires for additional information. Eighteen cases (20% of survivors) had active disease or reported previous reactivation at one of the follow ups. These comprised 50% of MS cases (10 MS RO-, 1 MS RO+) and 10% of SS cases (6 SS bone, and 1 SS skin). The shortest time to first recurrence of disease has been reported in those with MS or MF disease, and those with MF bone disease have a higher risk of reactivation compared to SS bone disease [94, 96, 101]. However, in this study none of the MF bone cases had active disease or a report of reactivation at follow up. In a study of 278 cases with SS disease, there was no difference in disease reactivation between those with UF and MF bone disease (18% in each), and it was suggested that early systemic therapy may have restricted reactivation in MF cases [58]. In this study, 6/10 MF bone cases had been treated on LCH protocol lending some credence to this theory.

Of those where reactivation had been reported (in 12% of surviving cases), eight children had reactivated disease at the first follow up and six at the second follow up, with three cases recurring. In studies in Stockholm, California and Argentina the proportions were higher – 18%, 49% and 30% respectively although the follow up periods were longer [96, 97, 101]. In line with other reports, the majority of reactivations were in cases with MS disease, except for one SS skin case, and their median age at diagnosis was 1.8 years [94, 101]. In a large study of 300 cases in Argentina the reactivation rate was 48% for MS cases, comparable with 41% MS in this study. However, the SS rate was much higher in Argentina [96] (17% versus 2%) although in the present study there was a larger proportion of SS cases. Similarly, 17% of paediatric bone cases in a Scottish study had progression of disease [107]. In contrast, Jubran et al found a low rate of reactivation in SS bone cases – 7.6% [94]. As in other reports, reactivation occurred mainly in existing sites of skin and bone [96], although it

developed in new sites in six cases – spleen (1), bone (3), skin (1), diabetes insipidus (5).

Three cases progressed, including one from SS bone to MS RO-, an event which is reportedly rare [58]. However, Bernstrand et al reported progression in 12/49 cases (6 SS and 6 MS), 75% of which, unlike the cases in this study, changed stage within six months of diagnosis [97].

The time from disease resolution to first reactivation is reported to be very variable, ranging from a few months to 27 years [58, 96-98, 101]. In addition, although reactivation often occurs within two years after no active disease, attaining resolution may also take considerable time. The range was 1 month to 7.5 years for MS cases in an International LCH Registry study, with 88% achieving resolution within two years after diagnosis [98]. With the relatively short duration of follow up in this study, it is likely that some cases will continue to experience reactivation or progression. Since reactivation is associated with increased risk of permanent consequences (as discussed below) further follow ups would be valuable to obtain comparable reactivation data and better estimations of disease-free survival.

7.7.2 Permanent consequences

At the first follow up, 20 cases (23%) had sequelae, and 16 cases (21%) had sequelae at the second. The proportions were similar in a national study in Denmark (27%) and multicentre study in France (22%) although lower than in Argentina (38%) [1, 56, 96]. However, only 11 cases with sequelae were reported at both follow ups. The differences, described in section 6.11.3, were mainly due to changes in reports of orthopaedic cases and the loss of a MS case who developed DI post-diagnosis. The probability of sequelae-free survival (excluding those diagnosed with diabetes insipidus) was 64% (CI: 37-82%) at 5 years, the addition of one case having the effect of reducing this to 21% (CI: 12-59%) at the maximum follow up period (6.2 years). Those with the lowest probability of being sequelae-free at five years were MS cases (42%), those treated on LCH protocol (40%) and those who took longest to diagnose, i.e. more than 6 months (29%). However, the number of cases in each of these subgroups was extremely small. As might be expected in cases with more extensive disease and treatment, previous studies have reported that MS and MF bone cases were

most at risk although only one MF bone case in this study had permanent consequences [58, 96, 101, 102].

Diabetes insipidus was the main permanent consequence in 12 cases (13%) cases which is comparable with other studies [56, 73, 96, 97] although reports by a French nationwide study and the Histiocyte Society were higher (both 24%). It is more common in MS cases [73, 97, 102], as was found in this study – 9/12 cases had MS disease.

DI developed after the original diagnosis in five cases and was the only permanent consequence in six. There is up to a 50% higher risk of DI if the skull or facial bones are involved [73, 102, 240]. 40% of the study group had skull, mandible, facial or orbit bone involvement at diagnosis (22 SS, 1MF and 14 MS RO-). However, only four of these had DI at diagnosis, two developing DI later on (i.e. 16% of those with skull involvement); this is comparable with Jubran et al (20%) but lower than other studies [94, 96, 102].

Of the five cases that developed DI post-diagnosis, two were reported to have DI at the first follow up and three cases were reported at the second follow up. All five had been treated on LCH protocol – four had MS disease and one had localised special site involvement (table 2.3) [74]. There has been conflicting evidence and debate as to whether systemic treatment will prevent progression to DI (and neurodegenerative disease which may not develop until many years later) [240-242]. In this study, treatment was not preventative. In addition, all five cases had reactivated disease in existing or new sites as well as DI, including other hormone deficiencies (2), bone lesions (3), skin (1) and lymph (1), and consequently received further treatment. New treatments may emerge when more is known about the mechanism of brain damage following inflammation elsewhere in the body, a topic which was the subject of this year's Nikolas Symposium (an annual think-tank of LCH scientists and doctors) [106].

As described above, endocrine and neurological problems have been associated with both DI and facial or skull bone involvement [96, 102, 241]. In keeping with these findings, all seven cases with growth failure or hormone deficiencies had DI; of three children with neurological problems, two had DI and the third had disease of the ears and nervous system. There were few orthopaedic sequelae (two cases) compared with

other reports (range 20%-42%) but as expected, very small numbers of other permanent consequences (table 6.20) [58, 101, 102]. Two bone cases had resolved spontaneously and five others had been discharged. The small number reported with orthopaedic sequelae may be due to the loss of ten SS bone cases in the final follow up. On the other hand it might be expected that any orthopaedic problems would have been brought to the attention of the treating clinician and sequelae consequently would have been reported.

Reactivation has been found to increase the risk of permanent consequences significantly [96, 98] and in this study 7/10 cases with sequelae (which were not present at diagnosis) had reported reactivation of disease.

The differences in rates and types of sequelae between the studies may be due to the length of follow up which increases the chance of finding permanent consequences. The median length of the final follow up was quite short (3.5 years) and as with reactivation, sequelae may develop long after the original diagnosis [102, 240, 242]. In a study by Bernstrand et al, at a median follow up time of 16 years, 42% had permanent consequences [97].

7.8 Deaths, survival and mortality

Three children (3.2%) with MS RO+ disease all died during the case ascertainment period and there were no further deaths during the follow up period. In France, the two-year survival rate among 258 cases was 99%, and in a Swedish study, 100% survival was reported in 29 cases with a median follow-up period of six years [3, 28]. In the Northwest of England over a 40-year period the 5-year survival rate was 71%. However, the rate improved over time, the 3-year survival rate (1985-1998) being 95%. The survival rate increased with age from 51% in those aged <1 year to 95% in those aged 5-15 years, those with liver or spleen disease having a higher risk [2]. In this study, the three children who died all had liver disease although in one case this was only identified microscopically post mortem. Jubran et al found that those aged <1 year with MS RO+ disease were at most risk of death, as was the case in this study [94]. Deaths over a 30 year period at GOSH and in Dublin were 13% and 21% respectively. Survival has improved over time due to international co-operation in clinical trials and implementation of treatment, and shared expertise.

Of the three deaths identified during the study period, only one was confirmed by ONS. All deaths in the UK should be registered between 5-14 days [243]. A lag in registration or loss may have occurred for unknown reasons although incomplete registration of neonatal deaths has been reported previously [244]. Anonymised deaths data from the RoI required further checking by the CSO. Three deaths notified were coded with an ICD-9 code which can be used for conditions other than LCH. On further examination of the text of the cause of death, only one of the three deaths was confirmed. (The other two deaths were from "Complex V mitochondrial disorder" and "Inherited defect in urea cycle metabolism".) In a recent study in France, which identified LCH deaths based on ICD codes, it was stated that the text of the cause of death was also checked [168]. This underlines the importance of obtaining textual information for the cause of death to avoid over-reporting.

In addition to the two unregistered deaths found in this survey, a further 18 deaths with LCH on the death certificate were identified over a 10-year period (1996-2005); all were under five years old. The sex ratio was 1.8:1. This is a little higher than in a study by Glass et al, of 270 deaths (1960-1964) of children with disseminated disease, in which the ratio was 1.4:1.

The age-standardized mortality rate was 1.91 per 10 million per year, aged 0-14 years. In France, the rate was comparable, decreasing from 1.0 per million per year between 1980-90, to 0.5 and 0.1 per million per year between 1990-99 and 1999-2005 respectively [168]. The decrease in mortality in children was thought to be due to more aggressive therapy over the years. In the UK and RoI, the highest number of deaths per year was four in 1999. Thereafter the number dropped to one per year from 2002 which may be consistent with this suggestion. In France, deaths data were obtained from the French national death certification centre and from the French LCH Registry. The difference in ASRs may be due to the different methods of ascertainment or the small number of cases.

7.9 Limitations of the data and questionnaires

The number of cases identified by this two-year survey was small because of the rarity of the disease. Consequently, this made meaningful interpretation of analyses difficult,

especially for follow ups. A longer survey period would have provided a larger cohort for analysis although would have been costly to obtain. In addition, the questionnaires varied in their completeness. For example, data on birth weights and the patient's first consultation were missing for a third of cases thus introducing the possibility of bias. However, there were relatively few inconsistencies and contradictory responses were readily resolved.

Inevitably there are aspects of the questionnaire design which could have been tackled differently with hindsight. For example, small improvements in the design of the questionnaire using closed questions for some questions, e.g. symptoms and investigations, may have helped both completion and analysis. Similarly, a single closed question on ethnicity using 2001 census criteria (which incorporates a mixed ethnicity group) may have been helpful. In addition, inclusion of a simple tick box in neonatal history may have clarified information, e.g., about twins, since the data on the three known twins was volunteered not requested. However, although there are advantages and disadvantages with both open and closed questions, valuable information was provided by clinicians in the open questions and additional text fields.

The amount and type of data collected by questionnaire in this survey was limited by the BPSU surveillance methods, mainly because they do not allow patient consent to be sought (because it would introduce delay and possible reporting bias). The questionnaire was designed to capture sufficient information to identify cases in the survey and although it was hoped that the results might give some indications for future studies it was not designed to look for risk factors. It was, therefore, a compromise. For example, the BPSU were reluctant to include questions on environmental exposures (section 3.7.2) which have been included in the Canadian paediatric survey [46]. However, although it would have been of interest to collect such information, the questionnaire was already several pages long and the burden of completion by clinicians was a consideration.

With hindsight it may have been wiser to have conducted a single follow up two years after diagnosis since one year allows too little time for sequelae to develop and to assess mortality, and is too short for meaningful outcomes. With regard to the follow up questionnaires, a snapshot of the disease status only was obtained. Information on whether patients had attained complete resolution of their disease would have been

desirable as the distinction between those with refractory and reactivated disease cannot be made nor comparisons made with other studies. In addition, although the change in format of the two year follow up questionnaire was designed to prompt speedy replies from clinicians – a strategy described in section 7.2.1 – the information received may have been less informative. A single, more detailed follow up questionnaire sent two years after diagnosis may have elicited better data.

The results obtained have, however, generated ideas for future studies which are outlined in the final chapter.

Chapter 8. Conclusions and recommendations

8.1 What the study adds

The epidemiology of LCH is under-studied and thus any information about the disease may be regarded as novel. This is the first study to report the incidence and mortality rates of LCH in children in the UK and Ireland. It is also the first national study of incidence to have used a well-established prospective method of surveillance with additional sources of ascertainment, the importance of which were demonstrated. In addition, the spectrum of disease among the population was described, and event-free survival and mortality were assessed.

8.2 Summary of strengths and weaknesses

The study benefited from using three sources of cases to maximize ascertainment, and although probably incomplete, it was comparable with other studies. The study was particularly effective in collecting cases of SS bone disease. The prospective method of ascertainment and active follow up may also have been beneficial as data on newly ascertained cases are readily available. However, responses from clinicians were incomplete in terms of both questionnaire returns and questionnaire completion. The difficulty in diagnosis of some cases (the longest interval was 170 weeks) may have contributed to the incidence being under-estimated. The study may also have failed to identify a small number of those with milder forms, 16-17 year olds, and possibly, very young cases with skin disease thereby introducing a bias in case ascertainment. The number of cases and incomplete questionnaire data also has implications for meaningful interpretation of analyses.

8.3 Recommendations

In line with other authors it is recommended that registries and incidence studies record all sources of cases and include estimates of completeness of ascertainment, as well as incidence rates, in their publications [45, 187]. Specific registers for LCH have been established in France, Belgium and Germany, and several other European cancer registries register LCH cases, as described above. It would be desirable if all UK cancer registries consistently recorded cases of LCH. However, given that only one form of

the disease is regarded (coded) as a malignancy this seems unlikely, and thus it is recommended that a registry of all LCH cases in the UK should be established building on the work in this thesis.

8.3.1 UK LCH registry

Registries of diseases have recently come into focus in connection with concern over the lack of information and services for rare diseases. The Chief Medical Officer (CMO) reported the urgent need for more specialists, awareness and funding for rare or orphan conditions (i.e., those which affect <5 per 10,000 per year) [245]. There are over 6000 such conditions in the UK and the numbers of cases combined (estimated at three million) contribute significantly to morbidity and mortality in childhood. The CMO's report included a proposal for national registers to improve surveillance, planning and research. In June 2009, EU Health Ministers adopted a European Council Recommendation calling on Member States to develop and implement strategies for the treatment of rare diseases. In the light of both these recommendations, it is to be hoped that a national plan will emerge.

In the rest of Europe the plight of those with rare diseases has been recognised for several years. Projects with EU/French funding such as the Orphanet database and Professional Encyclopedia of expert services, Eurordis, and European rare disease conferences, have been initiated to improve awareness of orphan drugs, research, policy, funding, patient associations and events. At present,"specialised Centres of Reference (CR) for diagnoses or procedures of particular conditions" exist within the NHS, and there are also regional specialist services for genetic diseases [246]. The UK branch of Orphanet is based in Manchester. Rare Diseases UK, initiated by patient organisations of those affected by genetic disorders, has also been formed to develop and strengthen support for those with rare diseases. By including LCH on these and other web-sites such as cure4kids, the National Organization for Rare Disorders (NORD) and the US National Institute of Health Office of Rare Disease Research, access to good quality information has become easier.

In the UK, as well as the BPSU, other groups, such as the British Orphan Lung Disease Registry, have been established to carry out surveillance of rare diseases. Registries for numerous rare conditions have also been set up, e.g., for Fanconi anaemia, Wolf-Hirschhorn syndrome and Evans syndrome [247]. As well as describing patterns of

disease, registers with detailed case information can answer important questions for parents, such as their child's survival prospects, expected quality of life and reproductive prospects. They can also be used to develop more detailed aetiological epidemiology studies.

A UK registry may also include HLH and other histiocytoses since the incidence of these related diseases is currently unknown. An additional benefit of setting up a registry of all histiocytoses would be the contribution to two international databases of LCH and associated syndromes, Euro-Histio-Net and the Rare Histiocytic Disorders Registry in Toronto. Given the recent dissolution of the CCLG, it is unclear how UK cases would otherwise be contributed.

A number of adult cases of LCH were notified during this survey and it is likely that there are at least as many adults as children with LCH in the UK. An adult LCH registry is being established in Germany but the only national incidence data currently available are from the Belgian LCH Registry (IR 2.2 per million per year). A UK registry of all histiocytic cases would provide a sufficient number of cases and a range of information for further childhood LCH studies and allow long-term follow up. It would also enable the incidence of LCH to be estimated in adults, and the patterns of disease to be described. There have been no population-based studies of LCH in adults and publications have been mainly from single specialty clinics. Most children with LCH are seen by paediatric oncologists and services are well-established. However, adults may present to many different disciplines and services are less well co-ordinated. As highlighted by the CMO and others, there is a need for better awareness and management of adults with rare diseases cases, and for adolescents making the transition to adult services [49, 246].

Case ascertainment could be both retrospective and prospective, as in the Belgian LCH survey. Retrospective data collection, e.g. from 2003 (the start of this study) would provide a comparison with the incidence rate estimated in this study. New cases could be sought prospectively based on methods and experience gained in this survey. To ascertain adult cases, sources could be expanded to include, for example, adult orthopaedic hospitals, bone tumour registries, lung transplant centres and societies of dermatologists and endocrinologists. Patient identifiable data would be required to avoid duplication, for cross-checking or linkage with other sources and for follow up.

Although many registries have an exemption from NIGB, patient consent may be required to enable fuller data (and tissue samples for other studies) to be collected. A mandatory minimum dataset for Euro-Histio-Net has been proposed but there are guidelines for much more extensive data collection (a form over 40 pages long).

A UK registry would ensure systematic collection of standardized data which would be compatible with children's cancer registries and Euro-Histio-Net. The objectives of the registry would have to be clearly established and justified since other kinds of data collection may suffice for different applications, e.g. ad hoc surveys, such as this study, or clinical trials. However, a major reason for creating any registry is to carry out long-term follow up. Establishment of a registry is complex. In addition to ascertainment of cases, consideration would need to be given to the regulatory issues of ethical approval, patient consent, confidentiality and data security, as well as data validation, follow up procedures, statistical analyses, access to medical records, dissemination of information and data sharing, plus continuous staffing and funding.

8.3.2 Further studies

The study has generated several ideas for future studies, assuming that larger numbers and more detailed information are available.

Risk factors

The two large US case-control studies, although not consistent in their findings, described several associations with LCH (section 2.5.1) [141, 142]. They used clinical notes and a 22-page questionnaire which was comprehensive in its coverage of potential risk factors. It may be difficult and of limited usefulness to try to replicate these studies but they made other interesting observations which may warrant further investigation. For example, in the study by Bhatia et al, although adjusting for the higher socioeconomic status of the LCH cases (all parents were members of The Histiocytosis Association), the possibility of selection bias could not be ruled out. Only part of the postcode was obtained in this study, to aid identification of cases. However, the full postcode would have enabled an assessment of socioeconomic status (by obtaining Townsend scores linked to postcodes and wards). It is possible that lower social class patients are less likely to present early and may be associated with diagnostic delay and more advanced disease which may affect the long-term outcome [248]. Full postcode

data would also allow geographic factors such as urban and rural differences to be investigated, and with sufficient numbers and a long timescale, cluster analysis.

In addition, it was noted in the study by Hamre et al that the offspring of all five mothers who gave birth aged over 41 years were diagnosed with disseminated disease under two years of age [142]. Examination of parental ages would therefore be of interest, as would parental occupations, smoking and other environmental factors. It is notable that these factors are included in the Canadian Paediatric Surveillance of LCH (begun 2009) which is based on this study.

Several studies have pointed to both genetic and environmental factors in the aetiology of LCH. As has been suggested, an epigenetic mechanism – an environmental factor causing a heritable change in gene function (though not a change in DNA code) – would support familial cases and spontaneous regression as well as LCH being an abnormal immune response to an infection [146]. A large study collecting data on maternal and childhood illnesses and infections may be warranted, as well as data on twins and those conceived via ART, as mentioned in section 7.6.3. As discussed in sections 7.6.1 and 7.6.2, any possible associations with seasonality and ethnicity may also be confirmed in with a larger cohort.

Follow up studies

The outcome of the disease is the main concern of parents of children with LCH. Survival data from UK clinical trials are available for those with the more severe forms of the disease. However, long-term follow up of all types of cases would provide more accurate information on co-morbidities, disease activity and permanent consequences, particularly since the latter events may be protracted.

Quality of life studies on patients with LCH have been carried out and there is some expertise in this area in the UK [100, 110, 249]. Although these studies have mainly concentrated on physical and cognitive function and behaviour, children with LCH have been found to have more anxiety and depression when compared with normative data [249]. A large study of children in the UK remains to be carried out and could additionally examine the reasons why some areas of quality of life are affected in this patient group.

Since little is known about the outcome of LCH in adolescents as they move to adult services, a study of young adults would also be of interest. Super et al described two teenage cases highlighting several issues in treating adolescents, including the need for appropriate information, confidentiality, support groups, smoking and compliance [250]. Long-term follow up of this group may usefully inform parents and teenagers of other patients' experiences as well as assess clinical outcome. Data on a national scale would be needed as the incidence rate reported in the Northern Region was 0.3 per million per year, aged 15-24 years [25]. Cases could be cross-checked with the TYA database at the Christie Hospital in Manchester.

Collaborative studies

Collaboration with other groups, in addition to providing larger numbers for analysis, may also give clues to the aetiology of LCH by comparing patterns of disease. For example, as referred to in section 2.5.4, for unknown reasons, the occurrence of liver and lung disease is much higher in South America. There are, however, reportedly higher rates of other lung diseases in urban areas of South America which may indicate ethnic or environmental differences [251, 252].

In the absence of a UK registry, further studies may be conducted using data from the Northern Region Young Person's Malignancy Disease Registry (NRYPMDR), based in Newcastle, and other children's cancer registries in the UK. The NRYPMDR registered 70 cases between 1968-2009, the Northwest registry registered 101 cases between 1954-1998, the West Midlands registry has registered 133 cases since 1954 and the Southwest registry has 16 cases from 2002-2006 [2, 21, 25, 253]. There is a fifth children's cancer registry – the Yorkshire Specialist Register of Cancer in Children and Young People – however, only LCH cases coded as a malignancy have been registered [254].

Finally, one of the objectives of this study was that it would contribute to a wider investigation involving Canada and the Netherlands. As mentioned above, a survey is underway in Canada and it is hoped that data will be combined in due course.

Appendix A WHO classification of diseases (ICD-10) – LCH in relation to cancers, leukaemias and other haematopoietic disorders

C00-C97 MALIGNANT NEOPLASMS

C00-C75 Malignant neoplasms, stated or presumed to be primary, of specified sites, except of lymphoid, haematopoietic and related tissue

C75-C81 Malignant neoplasms of ill-defined, secondary and unspecified sites; stated or presumed to be primary,of lymphoid, haematopoietic and related tissue; of independent (primary) multiple sites

C81-C96 Malignant neoplasms of lymphoid, haematopoietic and related tissue

- C81 Hodgkin's Disease
- C82 Follicular [nodular] non-Hodgkin's lymphoma
- C83 Diffuse non-Hodgkin's lymphoma
- C84 Peripheral and cutaneous T-cell lymphomas
- C85 Other and unspecified types of non-Hodgkin's lymphoma
- C88 Malignant immunoproliferative diseases
- C90 Multiple myeloma and malignant plasma cell neoplasms
- C91 Lymphoid leukaemia
- C92 Myeloid leukaemia
- C93 Monocytic leukaemia
- C94 Other leukaemias of specified cell type
- C95 Leukaemia of unspecified cell type
- **C96 Other and unspecified malignant neoplasms of lymphoid, haematopoietic and related tissue**
  - **C96.0 Letterer-Siwe disease**
  - C96.1 Malignant histiocytosis
  - C96.2 Malignant mast cell tumour
  - C96.3 True histiocytic lymphoma
  - C96.7 Other specified malignant neoplasms of lymphoid, haematopoietic and related tissue
  - C96.9 Malignant neoplasm of lymphoid, haematopoietic and related tissue, unspecified

D00-D48 IN SITU AND BENIGN NEOPLASMS AND NEOPLASMS OF UNCERTAIN OR UNKNOWN BEHAVIOUR

D50-D89 DISEASES OF THE BLOOD AND BLOOD-FORMING ORGANS AND CERTAIN DISORDERS INVOLVING THE IMMUNE MECHANISM

D50-D70 Nutritional, haemolytic, aplastic anaemias; Coagulation defects, purpura, other haemorrhagic conditions

D70-D77 Other diseases of blood and blood-forming organs

- D70 Agranulocytosis
- D71 Functional disorders of polymorphonuclear neutrophils eg Chronic granulomatous disease
- D72 Other disorders of white blood cells eg Eosinophilia
- D73 Diseases of spleen
- D74 Methaemoglobinaemia
- D75 Other diseases of blood and blood-forming organs
- **D76 Certain diseases involving lymphoreticular tissue and reticulohistiocytic system**
  - **D76.0 Langerhans' cell histiocytosis, not elsewhere classified – Eosinophilic granuloma; Hand-Schüller-Christian disease; Histiocytosis X (chronic)**
  - D76.1 Haemophagocytic lymphohistiocytosis
  - D76.2 Haemophagocytic syndrome, infection-associated
  - D76.3 Other histiocytosis syndromes; Reticulohistiocytoma; Sinus histiocytosis; Xanthogranuloma
- D77 Other disorders of blood and blood-forming organs in diseases classified elsewhere

D80 -D89 Certain disorders involving the immune mechanism

Appendix B Literature research strategy

A computerised search of the literature from 1950-2010 was carried out using SCOPUS, Medline, PubMed and ZETOC with no language restriction. In addition, selected medical journals, in particular, Paediatric Blood and Cancer, were reviewed as were abstracts of the proceedings of the annual meetings of the Histiocyte Society and publications by key authors in the field.

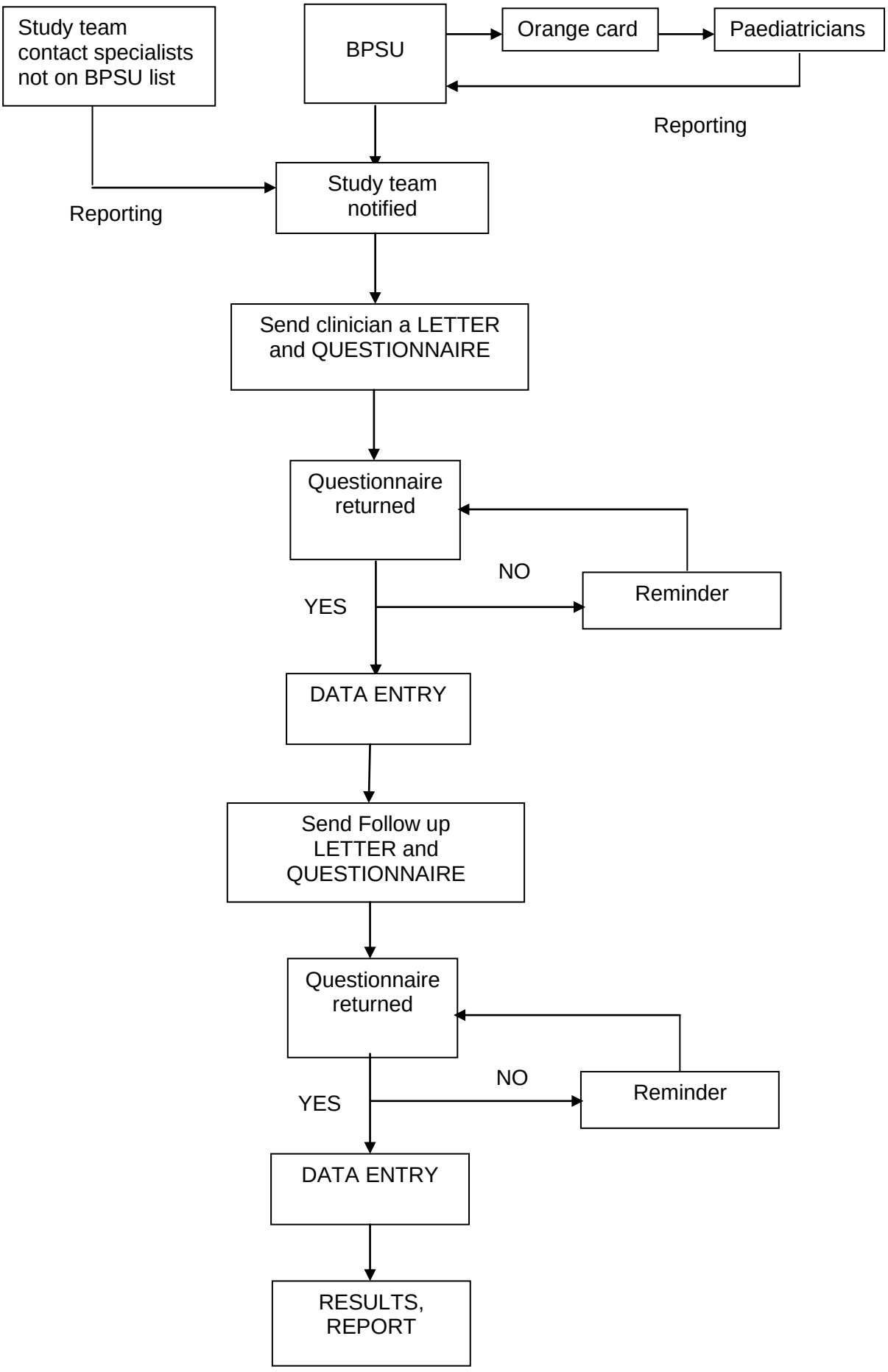
Keywords included all forms of the disease – Langerhans cell histiocytosis, eosinophilic granuloma, Hand-Schuller-Christian disease, Letterer-Siwe disease, Histiocytosis X, infantile acute reticuloendotheliosis, Hashimoto–Pritzker disease and Langerhans cell granulomatosis. Using the link word 'AND' keywords were searched with the following MESH (Medical Subject Heading) terms: classification, congenital, diagnosis, drug therapy, epidemiology, aetiology, genetics, history, immunology, mortality, pathology, physiopathology, radiotherapy, surgery, therapy, virology. Variations in spellings were taken into account by using free text terms as well as MESH terms.

Keywords were also combined with other search terms including: child, adult, infant, incidence, prevalence, risk factor, follow up, morbidity, reactivation, recurrence, neoplasm, registries, cancer registry, treatment, sequelae, in vitro fertilisation, diabetes insipidus.

The titles of all retrieved articles were reviewed and the full texts of relevant publications were obtained. Reference lists from the selected publications were checked for any papers of interest not previously identified.

Further information, electronic reports and data were obtained from the web-sites of various organisations and institutions such as the Department of Health, ONS, Orphanet and Rare Diseases Taskforce.

Appendix C Methods flowchart



Appendix D BPSU response form

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Tel: 020 7323 7912 Fax: 020 7323 7901
Email: Jennifer.Ellinghaus@rcpch.ac.uk

Professor L Parker
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Notification of Case Reported

BPSU Case Ref: LC/0506/08

Respondent Ref: 9511RU

Date: 01/07/2004

Reported by:
Dr
Royal United Hospital
Coombe Park
Bath
BA1 3NG

Please complete the result follow up section below as soon as you have the information requested, save this document and return it by **reattaching the saved version** to an email to Jennifer.Ellinghaus@rcpch.ac.uk or via post to the address listed above. If you have any queries, please contact the BPSU Research Administrator.
✂

Result of Follow Up LC/0506/08 9511RU
Please mark the appropriate box with an X:

	Case confirmed (C)
	Possible (P)
	Already known (R) (please give source at * below)
	Duplicate confirmed (DP) (please give previous case ref. at * below)
	Duplicate not confirmed (DN) (please give previous case ref. at * below)
	No case / error (E) (please give details at * below)
	Unable to follow up (UF) (please give details at * below)

*** Please give details here:**

Any additional comments:

Regards

J. Ellinghaus

Jennifer Ellinghaus
BPSU Research Administrator

Appendix E List of sources for compilation of Newcastle mailing list

Children's Cancer and Leukaemia Group (formerly UK Children's Cancer Study Group) members list

British Paediatric Rheumatology Group

British Society for Paediatric Dermatology

British Association for Paediatric Nephrology

Royal College of Pathologists

The Medical Directory 2000, Informa Healthcare, Informa Publishing Group 2000

Irish Medical Directory, 7th Edition. Medical Information Systems 2000

Hospital and institution web pages

www. specialistinfo.com

Appendix F Letter and form used in Newcastle survey

Dear Dr

Surveillance of Langerhans Cell Histiocytosis (LCH) in the UK and Ireland

We are carrying out the above two year study in association with the British Paediatric Surveillance Unit of the Royal College of Paediatrics and Child Health (RCPCH). The study has been approved by the London Multi-centre Research Ethics Committee and a copy of the approval letter is enclosed.

We are aware that clinicians who may not be members of RCPCH may come across adults and children with this disease. We would like to ascertain as many cases as possible and are therefore writing to ask you to inform us of any newly-diagnosed cases of Langerhans Cell Histiocytosis (LCH) that you have seen during 1.6.03 - 30.11.03. I enclose a leaflet about the disease for your information.

I should be very grateful if you would complete the slip at the bottom of this letter and return it to me in the enclosed pre-paid envelope. If you have seen a newly-diagnosed case of LCH during this period, we will send you a questionnaire to obtain further details.

Please do not hesitate to contact me if you have any questions about the study. If you need any clinical advice regarding the eligibility of a particular case for inclusion in the study, please contact Dr Vasanta Nanduri or Dr Kevin Windebank (telephone numbers and addresses are shown on the leaflet).

We will contact you again in six months time. My apologies for any cross-posting.

With many thanks for your help,
Yours sincerely,

Prof Louise Parker
Professor in Paediatric Epidemiology E-mail:louise.parker@ncl.ac.uk

---

<Doctor ID> SURVEY OF LANGERHANS CELL HISTIOCYTOSIS – 1.6.03 - 30.11.03

I have/have not seen a new case of LCH. Number of definite cases ☐

Number of probable cases ☐ Adult cases YES/NO

Signed: …… Date: …….

Name: ……..

Appendix G Letter to reporting clinicians for further information

Dear Dr

Re: Surveillance of Langerhans Cell Histiocytosis (LCH) in the United Kingdom and Ireland in association with the British Paediatric Surveillance Unit.

Thank you for notifying a case for this study through the British Paediatric Surveillance Unit of the Royal College of Paediatrics and Child Health.

I am now writing to gather further information about this case, using the enclosed questionnaire. I should be very grateful if you could complete it and return it to me in the enclosed reply paid envelope. Please return the questionnaire, even if there are some sections you are unable to complete.

The following information is sought:
- **demographic details**
- **referral pattern**
- **clinical presentation and diagnosis**

I will not be contacting your patient or his/her family at any time. Minimum identifying information is sought on your patient to avoid duplication. All information provided by you will be treated in strict confidence. The study has been approved by the London MREC (copy of approval attached).

Please do not hesitate to contact me if you have any questions about the questionnaire, or any aspect of the study. If you need any clinical advice regarding the eligibilityof a particular case for inclusion in the study please contact Dr Vasanta Nanduri or Dr Kevin Windebank (telephone numbers and addresses below).

I am grateful to you for reporting to the BPSU and for taking the time to provide further information about your patient(s). I will also ensure that you are sent a copy of the final report of the study.

With many thanks for your help,
Yours sincerely

Prof Louise Parker
Professor in Paediatric Epidemiology
Dept of Child Health, Sir James Spence Institute
Royal Victoria Infirmary, Victoria Road
Newcastle upon Tyne, NE1 4LP
Tel: 0191 202 3037
Email: louise.parker@ncl.ac.uk

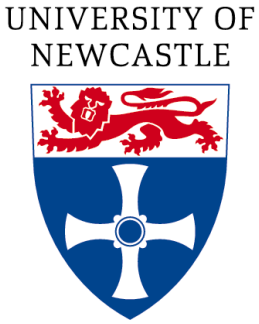
Contact details

Dr Vasanta Nanduri
Consultant Paediatrician and Oncologist
Watford General Hospital
Vicarage Road, Watford WD1 8HB
Tel: 01923 217992
Email: v_nanduri@hotmail.com
vasanta.nanduri@whht.nhs.uk

Dr Kevin Windebank
Consultant Paediatric Oncologist and Senior Lecturer
Dept of Child Health, Sir James Spence Institute
Royal Victoria Infirmary, Victoria Road
Newcastle upon Tyne, NE1 4LP

Tel: 0191 202 3037
E mail: k.p.windebank@ncl.ac.uk

Appendix H Questionnaire to reporting clinicians



Sir James Spence Institute, Newcastle upon Tyne
British Paediatric Surveillance Unit, London

SURVEY OF LANGERHANS CELL HISTIOCYTOSIS (LCH) IN THE UNITED KINGDOM AND IRELAND

For office Use

Study Number _____

BPSU Number _____

Questionnaire completed by _____

Consultant in charge, if not above _____

Hospital / Institution _____

Date of completion _____

SECTION A: PATIENT IDENTIFICATION DATA

HOSPITAL NUMBER: __/__/__/__/__/__/__/__/__/__

NHS NUMBER: __/__/__/__/__/__/__/__/__/__

DATE OF BIRTH (DD / MM / YY): ___ / ___ / ___

GENDER: MALE / FEMALE

POST CODE of current address (first half): ___ ___ ___ ___

SECTION B: FAMILY HISTORY

1. Country of Birth (Please tick)
☐ England
☐ Scotland
☐ Wales
☐ Northern Ireland
☐ Irish Republic
☐ Elsewhere
Please specify …….

2. Ethnic Origin (Please tick)
☐ White
☐ Black - Caribbean
☐ Black - African
☐ Black - other
Please specify …….
☐ Indian
☐ Pakistani
☐ Bangladeshi
☐ Chinese
☐ Any other ethnic group
Please specify …….

3. Parental consanguinity ☐Yes ☐No ☐Not known

4. Associated conditions

a. Maternal history of thyroid disease ☐Yes ☐No ☐Not known

b. Family history of LCH ☐Yes ☐No ☐Not known

If yes, relationship to patient and any other relevant details

……

……

SECTION C: PREGNANCY, DELIVERY AND NEONATAL HISTORY

1. Maternal health during pregnancy
   ☐ Hypertension
   ☐ Serious infection (requiring IV antibiotics, hospitalisation)
   ☐ Any other medical problems, please specify…….
   …….
2. Gestational age …….
3. Birth weight ……..

SECTION D: DIAGNOSIS

DATE OF DIAGNOSIS (DD /MM / YY): ___ / ___ / ___

(Date of biopsy or of clinical/ radiological diagnosis upon which management decisions were based.)

HISTOLOGY: Tissue ……..

	H&E	**S100**	**ATPase**	**P.Lectin**	**αMann**	**CD1A**	**Birbeck**
Positive							
Negative							
Not done							

SECTION E: REFERRAL HISTORY

1. Date of 1st symptom (DD/MM/YY) ___ / ___ / ___ a. Age at 1st symptom ……
2. Presenting symptom(s) (e.g. rash, lump, pain, fever, ear discharge, other)

……

……

……

3. Date of 1st visit to GP with initial symptoms DD/MM/YY ___ / ___ / ___

   Details…….……

4. Date of first referral to hospital (DD/MM/YY) ___ / ___ / ___ ☐ Not known
5. Date first seen in hospital (DD/MM/YY)
6. Referred to tertiary centre ☐ Yes ☐ No ☐ Not known

   If yes, details…….

7. Date seen at specialist / tertiary centre (DD/MM/YY) ___ / ___ / ___
8. Specialties referred to for LCH-related problems (Please tick all boxes that apply)

	Yes	Date, if known	No	Not known
Orthopaedic				
Paediatrics				
Dermatology				
Oncology				
ENT				
Ophthalmology				
Respiratory				
Endocrinology				
Other (specify)				

SECTION F: SYSTEM/S INVOLVED AND DIAGNOSTIC PROCEDURES (PLEASE TICK ALL THAT APPLY)

	At diagnosis			At any time			Diagnostic procedure e.g. X ray, scan, biopsy, relevant positives/negatives			
Bone	**Y**	**N**	**N/K**	**Y**	**N**	**N/K**	**Y**	**N**	**N/K**	**DETAILS**
Skin										
Ears										
Oral mucosa										
Bone marrow										
Liver										
Spleen										
Lymph node										
Lungs										
Gut										
Diab. Insipidus										
Ant. pituitary										
Genital mucosa										
Nervous system										
Other, specify										

SECTION G: STATUS

Does this child have any associated malignant disease (or has he/she had one in the past)?

☐ Yes ☐ No ☐ Not known

If yes, please specify ……..

Date of last follow up (DD/MM/YY) ___ / ___ / ___

Status at last follow up

☐ Alive, with no active disease ☐ Alive, with active disease ☐ Dead

If dead, date of death (DD/MM/YY) ___ / ___ / ___

Is the patient registered with UKCCSG? ☐Yes ☐ No ☐ Not known

Any other comments you wish to make

……

……

……

……

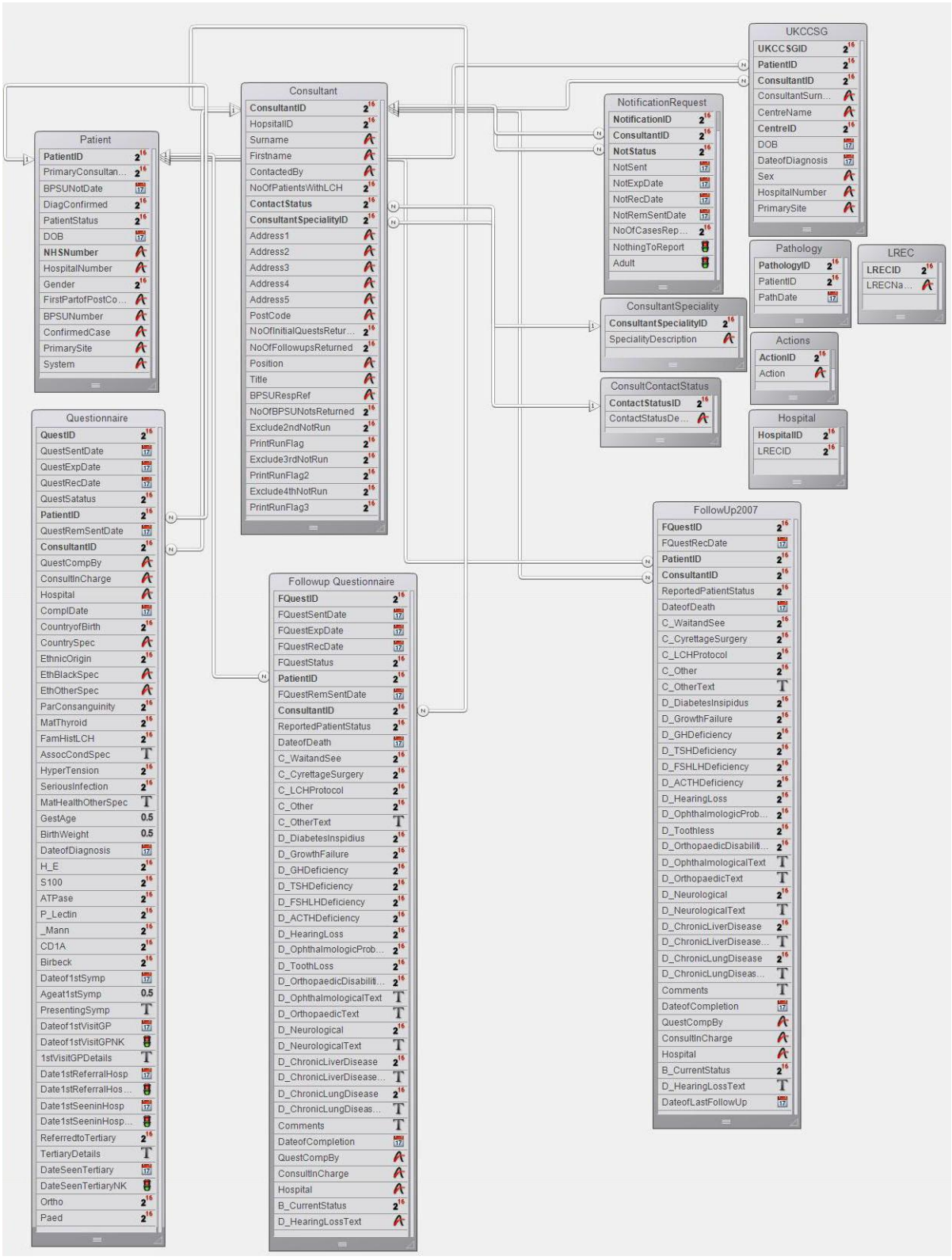
Thank you for your help

Please return in the reply paid envelope provided to Prof. Louise Parker, at the address below, who can be contacted by email or telephone if necessary:

Email: Louise.Parker@ncl.ac.uk Tel: 0191 202 3037

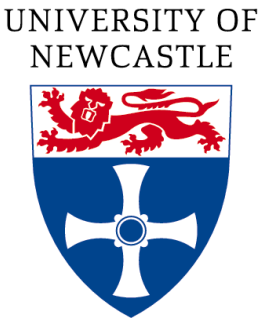
Prof. Louise Parker
Professor in Paediatric Epidemiology
School of Clinical Medical Sciences (Child Health)
University of Newcastle
Sir James Spence Institute
Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne
NE1 4LP

Appendix I Structure of the database



Questionnaire tables are truncated.

Appendix J First year follow up questionnaire



Sir James Spence Institute, Newcastle-upon-Tyne
British Paediatric Surveillance Unit, London

SURVEY OF LANGERHANS CELL HISTIOCYTOSIS (LCH) IN THE UNITED KINGDOM AND IRELAND - 1 year follow up

For office Use

Study Number _____

BPSU Number _____

Questionnaire completed by _____

Consultant in charge, if not above _____

HOSPITAL / INSTITUTION _____

Date of completion _____

SECTION A: PATIENT IDENTIFICATION DATA

1. HOSPITAL NUMBER: __/__/__/__/__/__/__/__/__/__

2. NHS NUMBER: __/__/__/__/__/__/__/__/__/__

3. DATE OF BIRTH (DD/MM /YY): ___ / ___ / ___

4. GENDER: MALE / FEMALE

5. POST CODE of current address: ___ ___ ___ Ist 3 characters only

SECTION B: CURRENT STATUS

☐ Alive, no active disease
☐ Alive, active disease
☐ Active disease, on treatment
☐ Dead
If dead, date of death (DD / MM / YY): ___ / ___ /___

SECTION C: TREATMENT

1. Wait and see	☐ Yes	☐ No	☐ Not Known
2. Curettage/surgery	☐ Yes	☐ No	☐ Not Known
3. LCH protocol	☐ Yes	☐ No	☐ Not Known
4. Other	☐ Yes	☐ No	☐ Not Known

Details……
……..

SECTION D: SEQUELAE / PERMANENT CONSEQUENCES

1. Diabetes insipidus:	☐ Yes	☐ No	☐ Not Known
2. Growth failure:	☐ Yes	☐ No	☐ Not Known
3. Anterior pituitary dysfunction:			
a. GH deficiency:	☐ Yes	☐ No	☐ Not Known
b. TSH deficiency:	☐ Yes	☐ No	☐ Not Known
c. FSH / LH deficiency:	☐ Yes	☐ No	☐ Not Known
d. ACTH deficiency	☐ Yes	☐ No	☐ Not Known
4. Hearing loss:	☐ Yes	☐ No	☐ Not Known

Conductive / Sensori-neural

5. Ophthalmologic problems	☐ Yes	☐ No	☐ Not Known

If yes, specify_____

6. Tooth loss	☐ Yes	☐ No	☐ Not Known

7.Orthopaedic disabilities	☐ Yes	☐ No	☐ Not Known

If yes, specify_____

8. Neurological consequences ☐ Yes ☐ No ☐ Not Known

If yes, specify_____

9. Chronic liver disease ☐ Yes ☐ No ☐ Not Known

If yes, specify_____

10.Chronic lung disease ☐ Yes ☐ No ☐ Not Known

If yes, specify_____

Any other comments you wish to make

……

……

……

Thank you for your help

Please return in the reply paid envelope provided to Prof. Louise Parker, at the address below, who can be contacted by email or telephone if necessary :

Email Louise.Parker@ncl.ac.uk Tel 0191 202 3023

Prof. Louise Parker
Professor in Paediatric Epidemiology
Dept of Child Health
University of Newcastle upon Tyne
Royal Victoria Infirmary
Queen Victoria Road
Newcastle, NE1 4LP

Appendix K Second year follow up questionnaire

SURVEY OF LANGERHANS CELL HISTIOCYTOSIS (LCH) IN THE UK AND IRELAND - Follow up - 2007

Consultant name **Hospital name**

PATIENT
Hospital Number
NHS Number
Date Of Birth
Gender Male/Female
Post Code of Current Address (First Half)

CURRENT STATUS	Please tick and give date of last follow up
Alive, no active disease	
Alive, active disease	
Active disease, on treatment	
Dead. *If dead, date of death*	
Not known	

TREATMENT STRATEGY	Please tick
Wait and see	
Curettage/ surgery	
LCH protocol	
Other. Please give details	

SEQUELAE	Please tick and/or circle
Growth failure	
Anterior pituitary dysfunction	Deficiency - GH TSH FSH/LH ACTH
Post pituitary dysfunction	
Hearing loss	
Ophthalmic problems	
Tooth loss	
Orthopaedic disabilities	
Neurological consequences	
Chronic liver disease	
Chronic lung disease	

Any other comments you wish to make:

Completed by: _____ Date of completion: _____
(if not name above)

Thank you for your help

Please return in the reply paid envelope provided to Dr Kevin Windebank, at the address below:
School of Clinical Medical Sciences (Child Health), University of Newcastle,
Sir James Spence Institute, Royal Victoria Infirmary, Queen Victoria Road,
Newcastle upon Tyne NE1 4LP

Appendix L Results of ascertainment using Epidat

Table 1. Two sources

	Missing cases	Total no. of cases	CI	Exhaustivity (%)			
				BPSU	NCL	CCLG	Total
BPSU versus NCL	14	102	91-113	67.48	56.72	-	86.06
BPSU versus CCLG	2	86	83-89	80.03	-	86.99	97.43
NCL versus CCLG	8	96	89-104	-	60.12	77.74	91.21

Table 2. Three sources – eight models

	Hypothesis	Estimate of $\hat{X}$	Estimate of $\hat{N}$	CI (95.0%)	G^2	df	BIC
1	A, B and C independent	2	96	93-99	15.93	3	7.81
2	A and B independent of C	2	96	93-100	15.93	2	10.52
3	**A and C independent of B**	**7**	**101**	**94-109**	**2.32**	**2**	**-3.09**
4	B and C independent of A	1	95	93-98	14.35	2	8.94
5	A independent of B	6	100	92-110	2.26	1	-0.45
6	A independent of C	1	95	93-98	14.28	1	11.58
7	B independent of C	20	114	83-145	0.00	1	-2.71
8	A, B and C dependent	20	114	75-153	0.00	0	0.00

Where A= CCLG, B= NCL, C= BPSU

$\hat{X}$ Estimation of the cases not notified by any registry
$\hat{N}$ Estimation of the total cases
df degrees of freedom
G^2 Likelihood ratio statistic (goodness of fit)
BIC Bayesian information criterion

Compared with figure 4.3 (Hook and Regal)
Models 2-4 are equivalent to two independent sources
Models 5-7 are equivalent to two independent subsets, e.g. model 5 is subset CCLG-BPSU independent of subset NCL-BPSU

Appendix M LCH cases and their inclusion in follow ups

Case ID	Sex	Type of disease		Date of birth	Date of diagnosis	1st Follow up	2nd Follow up
4	M	SS	Bone	09/10/1992	03/06/2003	Y	Y
5	M	SS	Bone	12/11/2002	11/06/2003	Y	Y
6	M	SS	Bone	04/06/1997	18/07/2003	Y	Y
7	M	SMF	Bone	02/12/1998	17/07/2003	Y	Y
17	M	MS	RO-	16/03/1994	17/09/2003	Y	Y
20	F	SS	Bone	27/09/1996	08/07/2003	Y	Y
21	M	MS	RO-	24/08/2001	10/10/2003	Y	Y
23	F	SS	Bone	27/01/2001	25/11/2003	Y	Y
26	M	SS	Lymph	09/07/1993	15/07/2003	Y	Y
28	M	SS	Bone	26/02/2000	08/12/2003	Y	Y
30	F	MS	RO-	24/05/1997	18/09/2003	Y	Y
31	M	SS	Bone	15/04/1995	14/10/2003	Y	Y
34	F	SS	Bone	05/05/1995	03/07/2003	Y	Y
38	F	SS	Bone	22/07/2002	27/11/2003	Y	Y
40	M	SS	Skin	05/11/2002	23/10/2003	Y	Y
41	F	SS	Bone	22/10/1997	26/01/2004	Y	Y
42	M	SS	Bone	27/05/1996	10/10/2003	Y	Y
43	F	MS	RO-	26/09/2003	23/01/2004	Y	Y
44	F	MS	RO+	01/06/2003	25/02/2004	Y	Y
45	M	MS	RO-	26/01/1994	11/09/2003	Y	Y
46	F	SS	Bone	30/11/1995	15/09/2003	Y	Y
47	M	SS	Bone	20/08/2000	18/06/2003	Y	Y
48	F	SS	Bone	09/05/1993	20/01/2004	Y	Y
49	M	MS	RO+	23/12/2003	27/01/2004	Dead	Dead
50	F	MS	RO-	08/05/2002	23/03/2004	Y	Y
51	F	SS	Bone	22/10/2003	11/03/2004	Y	Y
52	M	SMF	Bone	01/10/2002	02/05/2004	Y	Y
53	M	SS	Bone	10/05/1993	09/02/2004	Y	Y
55	M	SS	Bone	16/07/2000	21/04/2004	Y	Y
56	M	SMF	Bone	11/09/1994	26/03/2004	Y	Y
57	M	SS	Bone	19/04/2001	28/08/2003	Y	Lost to FUP
58	M	SS	Bone	15/01/1995	27/05/2004	Y	Y
59	M	MS	RO+	26/05/2003	21/04/2004	Y	Y
61	M	SS	Bone	31/05/1994	10/12/2003	Y	Y
62	M	MS	RO+	22/09/2002	04/06/2003	Dead	Dead
63	M	MS	RO-	04/04/2000	30/04/2004	Y	Lost to FUP
64	F	SS	Bone	01/03/1993	31/03/2004	Y	Changed diagnosis
65	F	MS	RO-	21/08/2003	01/04/2004	Y	Y
66	F	SS	Bone	25/10/1998	23/06/2004	Y	Y
67	M	MS	RO-	06/02/2003	07/04/2004	Y	Y

69	M	MS	RO-	01/03/2002	09/07/2004	Y	Y
70	F	SMF	Bone	15/10/1990	04/06/2004	Y	Y
71	F	SS	Bone	20/10/1994	28/06/2004	Y	Y
74	M	MS	RO+	03/03/2004	20/08/2004	Y	Y
75	M	SMF	Bone	02/02/1999	14/06/2004	Y	Y
76	M	MS	RO-	09/08/2003	20/08/2004	Y	Y
77	M	SS	Bone	09/01/2000	20/08/2004	Y	Lost to FUP
78	M	MS	RO-	21/01/2004	09/09/2004	Y	Y
80	F	SS	Bone	12/06/2003	07/05/2004	Y	Y
81	F	MS	RO-	07/10/2003	14/10/2004	Y	Y
82	M	SS	DI	26/08/1995	10/11/2004	Y	Y
85	M	SS	Bone	08/11/1988	15/01/2004	Y	Y
86	M	SS	Bone	01/03/2002	21/10/2004	Y	Y
88	M	SS	Bone	27/11/1994	02/02/2005	Y	Y
89	M	SS	Bone	25/10/2000	20/12/2004	Y	Excluded
90	M	SS	Bone	27/11/2003	11/01/2005	Excluded	Excluded
91	M	SS	Bone	29/06/1998	15/03/2005	Y	Y
92	F	SS	Bone	05/10/1995	09/03/2005	Y	Y
93	F	MS	RO+	31/03/2004	04/01/2005	Y	Y
94	M	SS	Bone	12/07/1998	13/08/2003	Y	Lost to FUP
95	M	SS	Bone	08/02/1990	30/12/2004	Y	Y
96	M	SS	Bone	22/05/1995	15/09/2003	Excluded	Lost to FUP
97	M	SS	Bone	23/10/1997	03/03/2005	Y	Lost to FUP
98	M	MS	RO-	06/07/1995	15/03/2005	Y	Y
99	M	MS	RO+	22/02/2004	12/01/2005	Dead	Dead
101	M	SS	Bone	13/12/1990	01/09/2004	Y	Y
102	M	MS	RO-	25/11/1995	08/02/2005	Y	Y
103	M	SS	Bone	04/03/1992	27/03/2004	Y	Y
104	F	SS	Lymph	27/02/1995	13/01/2004	Y	Y
105	M	MS	RO-	23/02/1999	15/04/2005	Y	Y
106	F	SS	Bone	02/11/1994	06/04/2005	Y	Y
107	M	SS	Bone	18/05/1994	29/03/2005	Y	Y
118	M	SMF	Bone	12/07/2000	02/12/2004	Y	Y
119	F	SMF	Bone	25/02/2002	06/01/2005	Y	Y
120	M	SS	Bone	06/01/1998	11/03/2005	Y	Y
121	M	SS	DI	18/07/1996	20/05/2005	Y	Y
122	M	SS	Bone	17/08/1992	10/05/2005	Y	Y
130	M	MS	RO-	05/08/1990	25/05/2005	Y	Y
131	F	SMF	Bone	21/03/2000	18/05/2005	Y	Y
132	F	SS	Skin	15/10/2004	01/12/2004	Y	Y
133	F	SS	Bone	11/05/2002	03/03/2005	Y	Y
135	F	SS	Bone	15/03/2001	21/06/2004	Y	Y
136	M	SS	Bone	11/05/2000	11/10/2004	Y	Y
140	F	SMF	Bone	23/04/2000	06/05/2005	Y	Y

141	F	SMF	Bone	02/10/2001	04/05/2005	Y	Y
142	F	SS	Bone	06/02/1997	03/05/2005	No reply	Y
143	M	SS	Bone	04/10/1991	19/01/2005	Excluded	Lost to FUP
144	F	SS	Bone	24/10/1994	01/06/2004	Y	Lost to FUP
145	F	SS	Bone	29/11/1995	28/02/2005	Y	Lost to FUP
146	F	SS	Bone	01/03/2003	14/04/2005	Excluded	Lost to FUP
147	F	SS	Bone	19/03/2001	20/04/2005	Y	147
149	F	SS	Bone	03/01/1997	27/05/2005	Y	149
150	M	SS	Bone	19/07/1998	01/05/2004	Y	150
151	F	MS	RO-	01/05/1999	24/07/2003	Y	151
Number of cases					94	86	78

Publications

1. Salotti JA, Nanduri V, Pearce MS, Parker L, Lynn RM, Windebank KP. *Incidence and clinical features of Langerhans cell histiocytosis in the UK and Ireland*. Archives of Disease in Childhood 2009, 94(5), 376-380.
2. Salotti, J. *Epidemiology of Langerhans cell histiocytosis: Onwards and upwards!* Pediatric Blood & Cancer 2008, 51(1), 3-4. (Highlight)
3. Salotti J, Windebank K, Nanduri V, Lynn R, Parker L. *An epidemiological survey of children with Langerhans Cell Histiocytosis in the UK and Eire, 2003-2006:* 23rd Annual Meeting of the Histiocyte Society 2007, Cambridge. Pediatric Blood & Cancer website 2008. (Abstract)
4. Salotti JA, Nanduri V, Pritchard J, Lynn R, Parker L, Windebank KP. *Langerhans Cell Histiocytosis (LCH) in children in the UK and Eire: an epidemiological survey. 22nd Annual Meeting of the Histiocyte Society 2006, Buenos Aires.* Pediatric Blood & Cancer 2007, 48(7)754. (Abstract)
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