BPSU

19th Annual Report 2004–2005

British Paediatric Surveillance Unit
Royal College of Paediatrics and Child Health

Aims of the British Paediatric Surveillance Unit

To:

- facilitate research into uncommon childhood infections and disorders for the advancement of knowledge and to effect practical improvement in prevention, treatment and service planning

- allow paediatricians to participate in surveillance of uncommon disorders and to lessen the burden on reporting doctors of such requests arising from numerous different sources

- increase awareness within the medical profession of the less common disorders studied and respond rapidly to public health emergencies.

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British Paediatric Surveillance Unit Annual Report 2004/2005

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Foreword

Dr Mike Preece
Chair, BPSU Committee

In last year's Foreword, I talked about two important initiatives: our application for funding from the Department of Health (DH); and our application to the Patient Information Advisory Group (PIAG) for approval to collect patient identifiable data without consent under the provisions of Section 60 of the Health and Social Care Act (2001). We have made considerable progress on both fronts.

Firstly, after helpful discussions with DH, we have been awarded 5 years funding of nearly £900,000, which will effectively cover the full running costs of the BPSU. However, additional funds are still required to allow us to offer the Sir Peter Tizard Research Bursary on an annual basis and to continue to honour our international obligations. One clear advantage of the funding is that we can now hold the costs to all investigators at the low level of £3,900 for a 13 month study. This secure funding also allows us to develop further the manner of working of the BPSU – for example we have undertaken to review the reporting process; would a web based system have advantages?

Secondly, we have just received notification of conditional approval from PIAG. This is accompanied with a timetable of changes to some types of studies that are required to meet the conditions. We will be working with the PIAG secretariat over the coming months in order to finalise this work. Each year we will need to re-present our studies for approval and all new studies will need to be submitted to PIAG, however they are willing to work with us to streamline this process.

Two new leaflets have now been produced: one for professionals and one for patients. The professional leaflet has recently been circulated with the College newsletter and the latter sent to paediatric Clinical Directors to be displayed in appropriate clinical areas. Copies of both leaflets are available from the BPSU office or can be viewed and downloaded from http://bpsu.inopsu.com/publicat.htm.

As in other years there have been changes to the Executive Committee, some have joined and some have left or are leaving. Dr Richard Reading, Dr Donal Manning and Dr Shankar Kanumakala have joined the committee. Dr Gabrielle Laing has stepped down after many years loyal service. Dr Hugh Davies is now unable to attend meetings because of other commitments. He is going to remain a corresponding member so that the Committee can access his considerable expertise in the workings of the Central Office of Research Ethics Committees (COREC). We are also losing Dr Bill Mcguire who is off to work in Australia.

There are also changes in the office. With the increased funding we have been able to appoint a full time BPSU research administrator, Jennifer Ellinghaus. Along with the rest of the Research Division the BPSU office has moved to new premises in Great Portland Street. However the orange cards and other correspondence should still be sent to the main College premises at 50 Hallam Street. With respect to the orange cards, we are concerned about a continued fall in response rate, which now hovers around 90% – 1% down on last year and our largest year on year fall to date. Once again, I exhort you to complete and return the cards on a regular basis.

On the international front, we continue to interact with INoPSU. We reported the 3rd meeting in Lisbon in last year's report and we shall host the 4th meeting in London in 2006. As communications liaison, Richard Lynn has commissioned a new INoPSU website which highlights the activities of all current INoPSU projects. Similarly, a task for the coming year is to upgrade our own website; any suggestions as to content are always welcome. The year 2006 will be our 20th year of surveillance and we intend to celebrate this with a symposium in May in London; details will be placed on the website as they develop.

Finally, I would like to thank all those that make the BPSU work: the members of the Executive Committee; Richard Lynn, the Scientific Coordinator; the administrative staff of the College; the investigators who initiate and execute the studies; but most of all the more than 2,500 paediatricians who complete the orange cards every month.

1 Introduction

Rare diseases and infections are, paradoxically, a numerically important cause of morbidity and mortality in childhood. Individually uncommon, together they number thousands, and many result in severe sequelae. Many are characterised by chronicity and by high rates of disabling sequelae or death. Most pose a large financial and emotional burden for affected children, their families and health systems.

To address this problem in the UK and Ireland in July 1986 the British Paediatric Surveillance Unit (BPSU) was set up, enabling paediatricians to participate in the surveillance and further study of uncommon disorders affecting children.

The Unit's main concern is that of epidemiological surveillance. This is defined as 'the collection, analysis and dissemination of high quality data relevant to the understanding, prevention and control of medical conditions of public health importance so as to satisfy the needs of health care professionals, science, government, voluntary organisations and the public at large'. (Adapted from: Bulletin of the World Health Organisation, 1994; 72).

Several agencies collaborate in the BPSU: the Royal College of Paediatrics and Child Health (RCPCH), the Health Protection Agency (HPA), the Centre for Paediatric Epidemiology and Biostatistics at the Institute of Child Health, London, Health Protection Scotland (HPS) which administers the scheme in Scotland and the Faculty of Paediatrics of the Royal College of Physicians of Ireland. As the BPSU monitors conditions of public health importance, an observer from the Department of Health attends the BPSU's Executive Committee, which meets every eight weeks to consider individual applications and the progress of studies.

The aims and key challenges of the Unit are summarised on the inside front cover.

This report mainly focuses on activities undertaken during the year 2004. Reference is also made to studies and activities which commenced in the year 2005.

2 How the surveillance system works

Selection of studies for inclusion in the scheme

A study is eligible for participation in the scheme if the subject is a rare childhood disorder (or rare complication of a more common disease) of such low incidence or prevalence as to require cases to be ascertained nationally in order to generate sufficient numbers for the study. All studies have to conform to high standards of scientific rigour and practicality. The system is open to any clinician or research group, but applicants are encouraged to approach the BPSU with, or through, a paediatrician or department of paediatrics/child health.

The number of conditions under surveillance is usually limited to 12 and there is keen competition for places on the BPSU card. The BPSU application procedure consists of two phases. Details on the BPSU application procedure can now be downloaded from the website at http://bpsu.inopsu.com/methodol.htm or are available on request from the BPSU office.

Factors that increase the likelihood of a study being accepted include scientific importance, rarity of the condition, proposals with outcomes of clear importance to public health and clear achievable objectives. Once approved by the BPSU Executive Committee, studies require Multi Research Ethics Committee (MREC) approval before commencement.

The reporting system

Those participating in the reporting system include consultant paediatricians who are either members of the RCPCH or the Faculty of Paediatrics of the Royal College of Physicians of Ireland.

Surveillance is 'active' in that the stimulus to report the orange card (Figure 1) comes from the Unit. Each month, all those participating in the scheme are sent an orange card listing the conditions currently under surveillance. A set of instructions for completing the card, including case definitions of the conditions listed on the card is also circulated. When a new study begins, the mailing also includes a specially produced study protocol card and other information about the study.

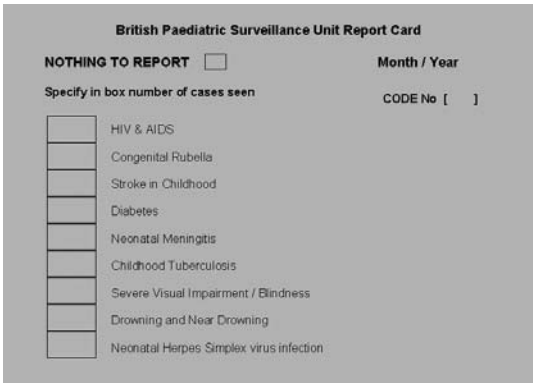

Figure 1: Orange Card

Respondents are asked to return the card to the BPSU office, indicating the number of cases of each condition on the card which they have seen during the preceding calendar month. Scottish paediatricians return their completed cards via Health Protection Scotland. When reporting a positive case, respondents are asked to complete the clinicians' tear-off section, making a note of the case and keeping the details for future reference. This is required because there have been occasions when clinicians have been contacted and they have been unable to recall the case.

Participants are expected to return cards even if they have no cases to report - there is a 'nothing to report' box on the card for them to tick. This is an important feature of the surveillance scheme as it allows non-responders to be identified. Follow-up reminders are sent to all participants in the scheme who have not returned their card for two consecutive months. Overall compliance rates are continually monitored. During this whole process at no time does the BPSU office receive patient details.

Follow-up and confirmation of case reports

On receiving a case report the BPSU informs the relevant investigating team who contact the reporting clinician for further information about the case, in accordance with the agreed protocol for the particular study. Particular care is taken to ensure that questionnaires sent to reporting clinicians are as short as possible, clear, straightforward and not excessive in their demands. The amount of patient identifiable data collected is strictly limited, though not to an extent that would compromise study aims.

The investigators subsequently report back to the BPSU on the outcome of each case follow-up, indicating when cases have been confirmed as meeting the case definition and identifying duplicate case reports (Figure 2). Duplication of reporting is most likely to occur when the condition requires referral to a tertiary unit but this is encouraged, as it is better to receive duplicates than miss the chance of receiving a report.

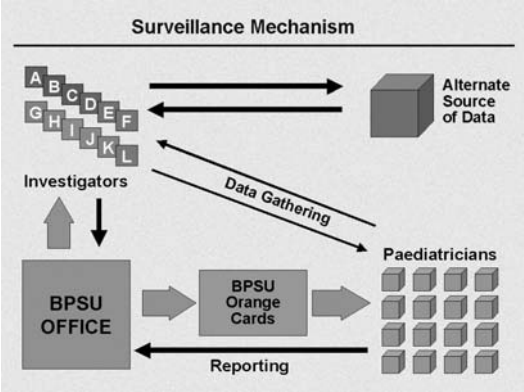

Figure 2: Surveillance Mechanism

The extent to which investigators receive survey data, identify incorrect reports and duplicates and the speed at which this is done is known as the 'completion rate'. Table 2 (page 6) shows the number of cases reported to the BPSU from its inception until the end of year 2004 for conditions under surveillance at October 2004. The number of cases which have so far been subsequently confirmed as meeting the case definition are also shown.

The time taken to follow-up a case report varies greatly between conditions and may be longer if microbiological or pathological details are required to confirm a case. The completion rate is high, for example, only 261 (3%) of the 7386 case reports have yet to be followed-up. As a study draws to a close this completion rate figure will rise. The final completion rate normally averages between 90-95%.

Table 3 and Table 4 (page 7) summarise the outcome of the follow-up of all cases reported to the BPSU by the end of year 2004 and provide evidence for the level of accuracy of reporting by participating clinicians.

Where necessary, to improve case ascertainment, consultants working in a number of other specialties have been invited to participate in the scheme. For example since 1992, pathologists who are not members of the RCPCH have also been included in the reporting scheme. In addition, most studies of infections use laboratory reports to microbiologists e.g. HIV/AIDS and congenital rubella. Apart from helping to improve ascertainment such complimentary data sources help to validate the surveillance system (Figure 3).

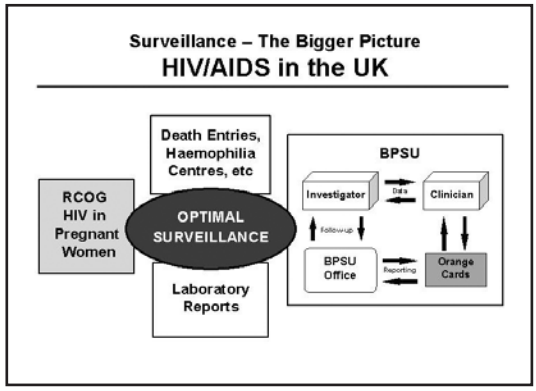

Figure 3: Surveillance - the bigger picture

Funding

For the three-year period to September 2004 the BPSU was in receipt of a grant from the Department of Health (DH). This grant has since been extended to 2009 and now covers the majority of the running costs of the unit. In addition, the BPSU asks surveillance teams to contribute a sum to cover the administrative costs of coordinating the study. This sum has now been reduced and is currently £3,900 for a 13-month study.

Further non-cost support is received from the Royal College of Paediatrics and Child Health, the Institute of Child Health (London), the Health Protection Agency (Communicable Disease Surveillance Unit) and Health Protection Scotland.

3 Scientific Coordinator's yearly review of activities

This past year has seen the commencement of four new BPSU studies, two of which are repeats of previous studies. In February a second study of neonatal herpes simplex virus (HSV) infection commenced for two years. June saw the commencement of a second study into medium chain acyl CoA dehydrogenase deficiency (MCADD). September saw the start of a study on thyrotoxicosis, the first study to be funded by the Sir Peter Tizard bursary. Finally, an RCPCH research division initiated project on non-type 1 diabetes in children commenced in October.

Five studies in 2004 had their period of surveillance extended for a further year: HIV/AIDS, congenital rubella, progressive intellectual and neurological deterioration, hyperbilirubinaemia and Langerhans cell histiocytosis. Only one study ended in 2004, this being invasive fungal infections in very low birth weight children (February). By December 2004, 58 studies had been completed since the BPSU's inception in June 1986 - those completed to June 2004 are listed in Appendix A. Known publications and presentations in 2004/2005 relating to these studies and the Unit's work totalled 37 and are listed in Appendices B and C.

Three studies have so far commenced in 2005; early onset eating disorders in children (March), Methicillin-resistant Staphylococcus aureus (MRSA) bacterimia (June) and scleroderma (July). The second Sir Peter Tizard Bursary award, to Dr Shamez Ladhani of the Royal London Hospital for surveillance into malaria, will commence once MREC approval has been received.

In-house, the Unit was successful in securing DH funding for a further five years, a major achievement. The BPSU continues to disseminate information on its activities to clinicians and the public alike. This is achieved mainly through this report, the quarterly bulletin and increasingly through the BPSU website. This site (http://bpsu.inopsu.com) now contains the definitive papers for completed BPSU studies. The site is also accessible through the RCPCH website at www.rcpch.ac.uk/research/bpsu.htm. This past year has also seen the production of a public information leaflet. Produced in conjunction with the RCPCH Patient and Carers Committee, this leaflet is available on-line and will be made available to clinicians to display in outpatient areas.

Richard Lynn
Scientific Coordinator
Photo by Joe Spinoza aged 8

The BPSU continues to contribute to the work of the International Network of Paediatric Surveillance Units. Following the successful INoPSU conference in Lisbon 2004 the BPSU undertook a revamp of the INoPSU website. This has now been completed and can be viewed at http://www.inopsu.com.

Participation in the scheme during the year 2004

The BPSU ascertains the names of new consultants primarily through the RCPCH advisory appointment committees, RCPCH membership office, through personal communication and the ongoing College workforce. During the year, 215 consultants were placed on the mailing list whilst 93 were removed, following retirement. The number of consultant paediatricians participating in the scheme during the year 2004 therefore rose to 2521, an increase of 6.7% on the previous year. It should be noted, however, that some paediatricians who hold consultant status are excluded, as they do not undertake relevant clinical work, or their colleagues report on their behalf. The BPSU mailing list also includes selected groups of consultants other than paediatricians such as cardiologists, clinical geneticists and pathologists. In order to help in the ascertainment of cases pathologists continue to be included in the surveillance system and our thanks are extended to the Royal College of Pathologists for supporting this initiative.

Reporting rates for returning the orange cards remain high. The overall card return compliance rate for the year 2004, calculated as a proportion of orange cards returned, was 91.2% (26,726 of 29,308), a fall of 1.1% from 2003. Monthly response rates ranged from 92.5% in January to 89.2% in June, with a median of 91.2%. In order to maintain this compliance rate respondents who have not returned cards for two consecutive months are sent letters, as much to verify postal address as to act as a reminder. Of those

responders not returning cards less than 2% are considered as persistent non-responders. The return rate remains higher than any equivalent UK scheme but only ranks 8 of the 14 other national paediatric units (Table 17, page 50).

Wales has once again achieved the highest average yearly response rate - 96.9% with South Scotland ranked second on 94.7%. The Thames area showed a cumulative response rate of 88.2% - a fall of 2.4% from 2003 (Figure 4). With so many teaching hospitals in London there is concern that cases may be going unreported.

However, it should be recognised that there are many paediatric specialists in London who receive the orange card but are never likely to see the conditions and thus may be less likely to return the cards on a regular basis, though we would encourage them to do so. With regard to rank order over the year, South Scotland rose 10 places to 2nd whilst Wessex rose eight places to 6th. North West Thames fell 15 places to 19th and Trent fell five places to 16th (Table 1). Despite the overall fall, the response to the system is still excellent.

Table 1: Regional response rate 2003 and 2004

Region	Rank 2004	Rank 2003
Northern	10	12
Yorkshire	4	6
Trent	16	11
East Anglia	14	16
NWT	19	4
NET	20	20
SET	17	17
SWT	15	18
Wessex	6	14
Oxford	7	5
South Western	12	9
West Midlands	11	8
Mersey	8	7
North Western	5	3
Wales	1	2
North Scotland	9	10
South Scotland	2	13
West Scotland	13	15
Northern Ireland	3	1
Republic of Ireland	18	19

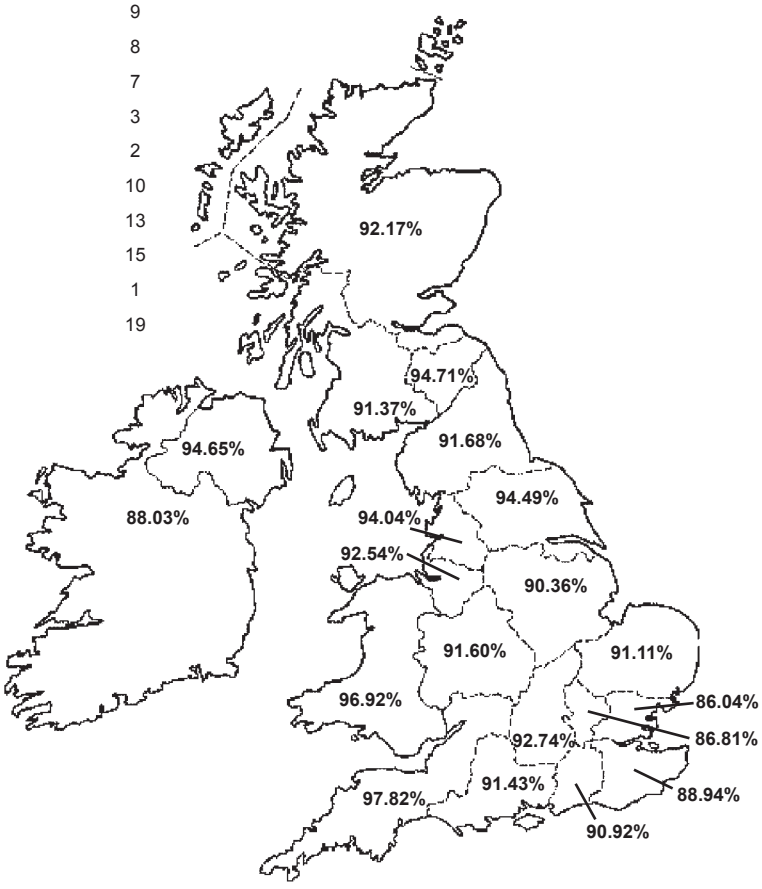

Figure 4: Average orange card return rate % by area

Workload of those reporting in the scheme

The BPSU continually monitors the workload of participants in the scheme in terms of the number of cases reported. 73% (1897) of participants reported no cases in 2004, 24.5% (634) reported between one and four cases and only 2.5% (64) reported five or more cases. The greatest number of cases reported were by HIV/AIDS specialists, one of whom reported 52 cases and another 106. Specialties that had a particularly high level of reporting were paediatric neurologists (PIND) and neonatologists (AIDS/HIV, tuberculosis in childhood and hyperbilirubinaemia in the newborn) who continue to carry the heaviest burden of reporting. Community paediatricians continue to make a significant contribution to the reporting scheme and their continued involvement is very much required and appreciated. With the continuation of the PIND and HIV/AIDS studies along with the eating disorder study this important contribution will continue in 2005.

Table 2: Cases reported from June 1986 – December 2004 for conditions under surveillance at June 2005 (cases confirmed by June 2005 shown in brackets)

		Reports (confirmed cases)				
	Date when reporting began	**June 1986-Dec-96**	**Jan-96 Dec-00**	**Jan-01 Dec-02**	**2003**	**2004**
Conditions under Surveillance						
HIV/AIDS	Jun-86	991 (691)	1017(704)	1042 (796)	732 (576)	688 (556)
Congenital rubella	Jun-91	72 (39)	49 (25)	19 (4)	7 (2)	2 (1)
PIND	May-97		1066 (635)	427(242)	183 (108)	177(126)
Congenital toxoplasmosis	Jul-01			16 (2)	14 (4)	11 (3)
Severe hyperbilirubinaemia	Jun-03				47 (24)	98 (62)
Langerhans cell histiocytosis	Jun-03				46 (14)	68 (36)
Childhood tuberculosis	Dec-03				51 (28)	483 (337)
Neonatal herpes simplex	Feb-04					61 (29)
MCADD	Jun-04					64(44)
Thyrotoxicosis	Sep-04					75 (37)
Non-type 1 diabetes	Oct-04					80 (37)
Total		**1063 (730)**	**2132 (1367)**	**1504 (1044)**	**1080 (756)**	**1807 (1268)**

HIV/AIDS Acquired immune deficiency syndrome/human immunodeficiency virus: reports of AIDS in June 1986 include cases previously seen; case definition extende to include HIV infection in January 1990

PIND Progressive Intellectual and Neurological Degeneration

MCADD Medium chain Acyl Co A dehydrogenase deficiency

Table 3: Outcome of follow-up of the cases reported in 2004 for conditions under surveillance at June 2004

Condition under surveillance	Date when reporting began	Valid reports	(%)	Invalid reports Duplicate	Invalid reports Errors	Total (%)	Not yet known	(%)	Total
HIV/AIDS	Jun-86	3,323	74	481	526	23	140	3	4470
Congenital rubella	Jun-91	71	48	26	50	51	2	1	149
PIND	May-97	1111	60	213	509	39	20	1	1853
Congenital toxoplasmosis*	Jul-02	9	22	4	22	63	6	15	41
Severe hyperbilirubinaemia	Jun-03	86	59	17	34	35	8	6	145
Langerhans cell histiocytosis	Jun-03	50	44	20	26	40	18	16	114
Childhood tuberculosis	Dec-03	365	68	54	93	28	22	4	534
Neonatal herpes simplex	Feb-04	29	48	9	14	38	9	15	61
MCADD	Jun-04	44	69	9	6	23	5	8	64
Thyrotoxicosis	Sep-04	37	49	3	19	29	16	21	75
Non-type 1 diabetes	Oct-04	37	46	1	27	35	15	19	80
All		**5162**	**68**	**837**	**1326**	**29**	**261**	**3**	**7586**

*Validation depends on microbiological/pathological details

Table 4: Case report table – classification of case reports

Valid reports:

Cases confirmed at follow-up as being both unique (i.e. not a duplicate) and satisfying the diagnostic criteria set out in the case definition. Confirmed cases reported to the BPSU but already known to the research worker from another source are included.

Invalid reports:

These include:

- duplicate reports of cases already reported to the BPSU,

  and

- reporting errors arising as a result of a misdiagnosis, the wrong box on the orange card being ticked, the case not meeting the diagnostic criteria set out in the case definition or an inability to follow-up a case.

Outcome not yet known:

Outcome of follow-up not yet received by BPSU (by June 2005).

4 Main findings of studies undertaken in 2004

Surveillance for **congenital rubella** (page 10) has been underway in the UK continuously since 1971. Eleven infants born since 1997 have been reported; in seven of these cases the maternal infection was acquired abroad. Although there is no evidence of rubella circulating in the UK at present, the uptake of MMR continues to be too low to maintain this situation in the longer term. Women who have come to the UK as adults have higher rates of rubella susceptibility than women who were born and brought up in the UK. They will be at higher risk of acquiring infection in pregnancy if rubella outbreaks occur.

Principal investigators: Dr P Tookey and Professor C Peckham, Dr E Miller - ICH London, HPA.

The BPSU survey of **HIV infection in children** (page 13) is the prime source of paediatric data on this condition in the UK and Ireland. Almost all new infections are acquired through mother to child transmission and although just over half of all reports continue to come from the London area, cases are increasingly being notified from all parts of the country. The prevalence of HIV infection in pregnant women in the UK and Ireland has increased substantially in recent years while the routine offer and recommendation of antenatal HIV testing has led to rising antenatal detection rates. It is not surprising therefore that reports of infants born to HIV infected women have also increased substantially while the proportion of infants who are themselves infected is declining.

Principal Investigators: Dr P Tookey, Dr F Ncube, Professor D Goldberg - ICH London, HPA, HPS.

After two years of surveillance the study on **hyperbilirubinaemia in the newborn** (>510 micromol/l) (page 31) ended in June. 86 cases have been confirmed to April 2005. 71 infants were readmitted from home for investigation and management of severe jaundice. 40 infants received a total of 46 exchange transfusions. Two infants died for whom co-morbidity (sepsis) may have been partly responsible.

Principal Investigators: Dr D Manning, Dr M J Platt - Arrowe Park Hospital, University of Liverpool.

The two-year surveillance of **Langerhans cell Histiocytosis (LCH)** (page 17) came to an end In June 2005. LCH is a rare multi-system disorder with a wide range of clinical presentations such as skin rash, bony lesions, hormone deficiencies or vital organ involvement. The course of the disease is unpredictable, varying from spontaneous regression and resolution to rapid progression and death, or repeated recurrence with risk of irreversible long-term disabilities. There have been 65 confirmed cases to date,
43 boys and 22 girls. As expected, children presented with varying features such as head swelling, rashes or skin lesions. Two children were diagnosed post-mortem.

Principal Investigators: Professor L Parker, Mrs J Salotti, Dr K Windebank, Dr V Naduri, Dr J Pritchard, Mr R Lynn - RVI Newcastle, GOS, RHSC Edinburgh, RCPCH.

Surveillance of **Medium chain acyl CoA dehydrogenase deficiency (MCADD)** (page 20) commenced in June 2004. The objectives of the study are to ascertain all cases of MCADD diagnosed during the study period in order to determine clinical outcome to two years of age with the aim of informing future national screening policy and to determine the detection rate of screening for MCADD in a UK setting. 79 cases have been reported so far of which 45 cases have been confirmed.

Principal Investigators: Professor C Dezateux, Dr J Oerton, Ms P Phillips, Dr G Shortland - ICH London, University Hospital Wales.

Surveillance of **Neonatal herpes simplex virus (HSV)** (page 23) infection commenced in February 2004 for a period of three years. It is proposed to ascertain the birth incidence of HSV disease, its clinical presentation and subsequent outcome. In the first year 23 cases were confirmed, virus was typed in all but one case. Maternal infection was not diagnosed prior to delivery in any case and 40% of mothers were under the age of 21 years.

Principal Investigators: Dr P Tookey, Professor C Peckham, Dr D Brown, Mr R Lynn - ICH London, HPA, RCPCH.

There is a growing body of evidence that the epidemic of obesity in UK children has resulted in a rising incidence of type 2 diabetes. Surveillance of **non-type 1 diabetes** (page 25) commenced in October 2004 to establish the clinical features that distinguish it from other forms of diabetes. In the first six months of surveillance 74 cases of non type 1 diabetes have been reported; these include cases of type 2, non-type 1 secondary to another condition and syndromic type 2 diabetes. Details of cases are being analysed to establish the incidence of obesity-related type 2 and how non-type 1 diabetes is being diagnosed and managed.

Principal Investigators: Mrs L Haines, Dr K Chong Wan, Mr R Lynn, Dr J Shields, Dr T Barrett - RCPCH, Bristol Royal Hospital for Sick Children, Birmingham Children's Hospital.

Despite the complexity of the conditions involved the survey of **progressive intellectual and neurological deterioration in children (PIND)** (page 28) has proved successful. It is being undertaken to identify cases of variant Creutzfeldt-Jakob disease in children in the UK. Over 1500 cases of suspected PIND have been reported. Among them 773 cases are confirmed diagnoses, comprising of 114 known degenerative conditions. Six cases of vCJD have been identified. Active surveillance continues into 2006.

Principal Investigators: Dr C Verity, Dr A-M Winstone, Mrs L Stellitano, Professor A Nicoll, Professor R Will - Addenbrooke's Hospital, HPA, CJDSU.

The surveillance of **symptomatic toxoplasmosis** (page 34), which commenced in July 2003, has now been ended after 24 months. 181 suspected cases have been reported. Of these 38 presented with symptoms or signs relating to definite or probable infection. Most of the confirmed cases of symptomatic toxoplasmosis were due to congenital infection.

Principal Investigators: Dr R Gilbert and Mr M Stanford - ICH London, Kings College Hospital.

After 13 months surveillance, the **tuberculosis in childhood** study (page 39) came to an end in December 2004. The study aimed to estimate the incidence of tuberculosis in the child population of the British Isles. Importantly it will also allow us to validate the enhanced surveillance system currently in place. 376 have been confirmed to date. Rates in London are considerably higher than other areas of the UK and Ireland.

Principal Investigators: Dr D Shingadia and Dr S Teo - Royal London Hospital.

October 2004 saw the commencement of the first study funded by the Sir Peter Tizard research bursary. A 13-month surveillance of **thyrotoxicosis in childhood** (page 43) is being undertaken to ascertain incidence, examine presenting features and consider how children are being managed. To date 35 cases have been confirmed, 74% were Graves's, 11% Hashimoto's and 3% congenital.

Principal Investigators: Dr S Williamson, and Dr S Greene - University of Dundee.

5 Surveillance studies undertaken in 2004

Congenital Rubella

Key Points

- Since 1997 only 10 congenital rubella births have been reported in the UK and one in Ireland.
- Seven of these were imported infections, with maternal infection acquired outside the British Isles.
- Although there is no evidence of rubella circulating at present, the uptake of MMR continues to be too low to maintain this situation in the longer term.
- Women who have come to the British Isles as adults are more likely than women who were born and/or brought up to be rubella susceptible. They will also be at higher risk of acquiring infection in pregnancy if rubella outbreaks occur.

Background

Rubella vaccination was introduced for schoolgirls in 1970 in the UK, and subsequently for susceptible women post-partum. The congenital rubella surveillance programme was established in Scotland, Wales and England in 1971 to monitor the effect of the vaccination strategy, and initially relied on passive reporting mainly from audiologists, paediatricians and microbiologists. The number of reported congenital rubella births and rubella associated terminations declined from an average of 50 births and 740 terminations a year in 1971-75 to 22 births and 54 terminations a year in 1986-90. Active surveillance through the BPSU started in 1990, and since then reports have also been received from Ireland and Northern Ireland.

Since 1988 the combined Measles, Mumps and Rubella vaccine (MMR) has been offered to all children in the second year of life; in 1996 a second dose of MMR was introduced for four year olds, and schoolgirl vaccination was discontinued. The circulation of wild rubella virus has been at extremely low levels in the UK in recent years, and an increasing proportion of individuals are protected by vaccine-induced immunity. However, adverse publicity about unproven associations between MMR, bowel disease and autism has led to a decline in MMR uptake since the mid 1990s, and in the last quarter of 2004 the recorded uptake for two year olds in the UK was only 81%[1]. The situation is similar in Ireland where MMR uptake is also low (83% in the last quarter of 2004[2]). If vaccine coverage does not improve it is possible that rubella could once again start to circulate in the British Isles, as it still does in many parts of the world.

The World Health Organisation Regional Office for Europe has set a target for the prevention of congenital rubella (<1 case per 100,000 births) by 2010[3], and sub-optimal MMR coverage and migration within Europe have been identified as major challenges to this target[4]. Awareness of rubella infection and congenital rubella among paediatricians and other health professionals must be maintained, and continued surveillance of congenital rubella is vital.

Objectives

To monitor the effectiveness of the rubella immunisation programme by determining the incidence of congenital rubella and investigating the circumstances surrounding any new cases.

Surveillance Period

Surveillance began in January 1990 and is reviewed annually.

Methodology

Case definition

Paediatricians are asked to report any infant (live or still born) or child up to 16 years of age who, in the opinion of the notifying paediatrician, has suspected or confirmed congenital rubella with or without defects, based on history, clinical, and/or laboratory findings. Included in this case definition are “imported cases”, including children born in the British isles where maternal infection occurred abroad.

Analysis

BPSU notifications - There was one confirmed notification of congenital rubella to the BPSU in 2004 - an infant born in Ireland whose mother had acquired infection abroad. Only one other additional report was received, relating to a child born in 1996 who had already been reported as an infant.

Since the beginning of active surveillance in 1990, 145 reports have been made through the BPSU (Table 5). Of the 129 reports from England, Scotland and Wales, 48 are confirmed or compatible, previously unreported cases of congenital rubella, four are possible cases, and 12 had already been reported from another source. The remaining reports were duplicates (20), reporting errors (40) and five where further information could not be obtained. Sixteen reports were from Northern Ireland or Ireland, and included four children with confirmed congenital rubella (one born in 1989, two in 1996 and the infant born in 2004), and a fifth possible case (born in 1983).

Congenital rubella 1990-2004 – Fifty-eight children with confirmed or compatible congenital rubella have been born and reported in the British Isles since the beginning of active surveillance in 1990, and 44 of these (76%) were first reported through the BPSU (Table 6, overleaf). Overall, about one-third of children born since 1990 had mothers who acquired infection abroad. Another third were born to women who, although they acquired infection in the British Isles, were recent immigrants[5,6]. Three British-born women had confirmed reinfection in pregnancy. There have also been 75 terminations for rubella disease or contact in pregnancy recorded by the Office for National Statistics in England and Wales during the period 1990-2003[7].

Recent reports

Eleven infants with congenital rubella were born and reported between 1999 and 2004, including one born in Ireland. Although seven (including the Irish case) were imported cases with maternal infection acquired abroad (three in Southern Asia, four in Africa), four infants were born to women whose infection occurred in the UK. One British-born woman acquired rubella in Scotland, although the infection was epidemiologically linked to an outbreak in Greece in 1999[8]. Three maternal infections were acquired in England, one by a British-born woman, and the other two by women from Sri Lanka, both of whom had been in the UK for several years.

Rubella susceptibility in pregnant women in the UK varies by ethnic group, with women from many parts of Asia and Africa having particularly high susceptibility rates especially if they are having their first baby[9]. Women who have come to the UK and Ireland from countries without comprehensive and long-standing vaccination programmes are likely to be at higher risk if there is renewed circulation of rubella here. Even while rubella infection is rare in the British Isles, susceptible women who travel abroad during early pregnancy may come into contact with infection.

It is essential that case ascertainment is as rapid and complete as possible, both for imported cases and those where infection was acquired in the UK or Ireland. Please notify to the BPSU all infants with suspected congenital rubella, whether or not they have the associated typical defects.

Table 5: Congenital rubella reports to BPSU 1990-2004 (includes births occurring in earlier years)

	Confirmed or compatible	Possible case	Cases already reported	Duplicate	Total error or lost
England, Scotland and Wales	48	4	12	65	129
NI and Ireland (all)	4	1	2	9	16

Table 6: Confirmed and compatible congenital rubella births reported in the UK and Ireland 1990-2004 (only includes births since 1990)

year of birth	Primary source of notification		Total
	BPSU	Other	
1990*	8	4	12
1991	2	1	3
1992**	5	2	7
1993	2	1	3
1994	5	2	7
1995	1	0	1
1996	11	3	14
1997	0	0	0
1998	0	0	0
1999	0	1	1
2000	4	0	4
2001	3	0	3
2002	0	0	0
2003	2	0	2
2004	1	0	1
Total	**44**	**14**	**58**

*Includes a stillborn infant
**Includes a set of triplets, one of whom was stillborn

Acknowledgements

We are extremely grateful to all participating paediatricians, especially those who have notified cases and completed questionnaires.

Funding

The Health Protection Agency makes a contribution towards the costs of the surveillance.

Ethics Approval

The London MREC reaffirmed approval in 2005.

Support Group

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HIV infection in childhood

Key Points

- Reports of infants born to HIV infected women have increased substantially year on year since 2000 but the proportion of infants born to HIV infected women who are themselves infected has declined.
- In spite of greatly improved antenatal detection rates, infants born in the British Isles to undiagnosed HIV infected women continue to present with symptomatic HIV infection themselves.
- A significant number of older children, often recently arrived from endemic areas, continue to be reported.
- Annual follow up of infected and indeterminate children continues.
- Uninfected children exposed to antiretroviral therapy in fetal life are being followed up in a separate MRC funded study (CHART) to explore whether there are any adverse effects of such exposure.

Background

National surveillance of paediatric HIV infection and AIDS began in 1986 and is based on independent but overlapping paediatric, obstetric and laboratory reporting schemes. All reporting is voluntary and confidential and data from all sources are combined as the National Study of HIV in Pregnancy and Childhood (NSHPC) at the Institute of Child Health[1].

Most children currently living with HIV in the UK and Ireland, whether born here or abroad, acquired their infection through mother to child transmission. Unlinked anonymous survey data[2] indicate that the number of births in the UK to HIV infected women (both diagnosed and undiagnosed) has increased substantially from about 300 in 1997 to about 860 in 2003. Antiretroviral treatment, delivery by elective caesarean section and the avoidance of breastfeeding reduce transmission rates to around 1% in comparison with a likely transmission rate of about 25% without interventions. In order for women to be able to access these interventions, the routine offer and recommendation of antenatal HIV testing to all pregnant women has been implemented throughout the UK and Ireland[3]. In the UK the proportion of women diagnosed before delivery increased from an estimated 32% in 1997 to about 90% in 2003.

Objective

The surveillance of paediatric HIV infection and AIDS in the United Kingdom and Ireland.

Surveillance Period

Surveillance began in June 1986 and is reviewed annually.

Methodology

Case definition

Any child less than 16 years of age who has AIDS, or is HIV antibody positive, or with positive virus culture, polymerase chain reaction (PCR) or antigen detection, or any other laboratory marker of HIV infection. Any child born to a woman known to be HIV infected at the time of that child's birth regardless of the child's infection status.

Alternative data sources

Additional data sources include paediatric reports made directly to the NSHPC (mainly from units caring for substantial numbers of infants born to infected women), obstetric reports made through a parallel obstetric reporting scheme run under the auspices of the Royal College of Obstetricians and Gynaecologists, laboratory reports to the Health Protection Agency, Centre for Infections and Health Protection Scotland, and children reported through the UK Haemophilia Centre.

Routine use of data

Summary data from the NSHPC are forwarded to the national surveillance centres on a quarterly basis, and contribute to the overall national surveillance of HIV infection. UK summary tables appear on a quarterly basis in the Communicable Disease Report (England, Wales and Northern Ireland - available at www.hpa.org.uk) and the Health Protection Scotland Weekly Report (available at www.hps.scot.nhs.uk).

Analysis

Number of reports: By the end of December 2004 there had been 4209 reports through the BPSU, of which 3030 were confirmed cases of HIV infection or infants at risk of vertical transmission, 524 were duplicates and 507 were reporting errors; the remaining 148 reports were still being investigated. A further 3235 confirmed cases were reported through other notification sources (see below). Table 7 shows the likely source of infection or exposure risk for all confirmed reports.

Children born abroad: Just over 10% (647) of all 6265 children ever reported in the UK and Ireland were born abroad and about 95% of these are known to be infected. Nearly two thirds of these children have had symptoms of HIV infection reported at some time and 29% have had an AIDS diagnosis: 59 are known to have died. Sixty two percent (400) of the 647 children born abroad have been notified since 2000 and nearly two thirds of these were at least five years old when first seen for care in the British Isles: the majority came from areas where HIV infection is endemic. In some cases it was not possible to ascertain the route of transmission as the HIV status of the mother at the time of the child's birth is unknown.

Follow up: Follow up information is sought for all infants born to infected women to establish their infection status, and all infected children are followed up annually to monitor their clinical and immunological status. Two hundred and fourteen infected children are known to have died and another 34 children died before their infection status could be established. Enhanced follow-up information for approximately 80% of infected children is currently collected through the Collaborative HIV Paediatric Study (CHIPS), a collaboration between the NSHPC, the MRC Clinical Trials Unit and participating clinics.

An increasing number of children, most of whom are uninfected, have been exposed to antiretroviral therapy (ART) in fetal or early life. Maintaining contact with these children is important in order to monitor any possible unwanted side effects of treatment; a consented follow up study of children exposed to ART (CHART) is underway with the help of reporting paediatricians and clinic staff [4].

Follow up of the surviving young adults infected in childhood during the course of treatment for haemophilia (all of whom were born before 1984) is undertaken by the UK Haemophilia Centre and the Health Protection Agency, Centre for Infections.

Table 7: HIV infection and infants born to HIV infected women (all reporting sources)
(notified by 31 December 2004)

Exposure / likely source of infection	BPSU reports	Reports from other sources	Total
Children born to HIV infected women	2930	2955	5885*
Likely source of infection for other infected children			
Haemophilia treatment	48	219	267
Blood transfusion/products	34	20	54
Other/not yet established	18	41	59
Total	**3030**	**3235**	**6265**

*1277 known to be infected (see table 8)

Table 8: Infection status of children born to HIV infected women (including children born abroad) (notified by 31 December 2004)

Region of first report	Infected	Indeterminate	Not infected	Total
London	797	606	1895	3298
Rest of England	342	399	780	1521
Wales & NI	16	20	24	60
Scotland	54	46	215	315
Ireland	68	196	427	691
Total	**1277**	**1267**	**3341**	**5885**

Footnote
** Over 100 additional births between 2000 and 2004 were reported in January 2005.
Nearly two thirds (38) of the 59 infected children born in the British Isles since the beginning of 2002 were born to undiagnosed women: nineteen of these children presented with AIDS, including three who died before six months of age, and seven presented with other symptoms of HIV infection.

Children born to infected women: Reports of children born to HIV infected women have increased substantially in recent years: over a third of the 5885 (Table 8) children ever notified were reported in 2003 and 2004. By the end of December 2004, 1277 children were known to be infected, and 3341 uninfected. Ten percent of all children born to infected women and over a third of the infected children were born abroad. Transmission rates cannot be estimated from these data as there is a bias towards the reporting of symptomatic children.

Ninety percent (5276) of vertically exposed children reported by the end of 2004 were born in the British Isles (Table 9) and over two thirds (3515) of these were born since 2000. (Table 8,**) Although the infection status of many of these infants has yet to be reported, the majority were born to diagnosed women and will themselves be uninfected.

Discussion

Reports of infants born to HIV infected women in the UK and Ireland have increased substantially each year since 2000. This pattern reflects both the increasing prevalence of HIV infection in pregnant women and the dramatic improvement in diagnosis rates following the implementation of routine antenatal screening throughout the British Isles. The majority of these infants were born to diagnosed women and will themselves be uninfected: while the number of diagnosed infected infants born in the British Isles each year has remained fairly constant since 2001 the proportion has substantially declined.

However, in spite of improved antenatal detection rates, infants born in the British Isles to undiagnosed women continue to present with symptomatic HIV infection and often an AIDS diagnosis. Deaths in young infants born here are still occurring as a result of their HIV infection.

HIV infected children born abroad continue to be reported. The majority of these children come from areas where HIV infection is endemic and most are diagnosed because they are unwell. It is not always possible to ascertain how they acquired HIV as often neither the child's medical history nor the mother's infection status is known.

Table 9: Year of birth and infection status of children born in the UK and Ireland to HIV infected women. (notified by 31 December 2004)

Year of Birth	Infected	Indeterminate	Not infected	Total
1982-1999	571	192	998	1761
2000	47	42	339	428
2001	29	88	471	588
2002	27	137	583	747
2003	24	300	668	992
2004*	8	499	253	760
Total	**706**	**1258**	**3312**	**5276**

*reports for this year expected to rise substantially

Funding

This study is funded by the Department of Health, and additional support is received from the collaborating institutions and the Medical Research Council.

Ethics Approval

The London Multicentre Research Ethics Committee reviewed and approved the NSHPC and the associated CHIPS and CHART study in 2004.

Support Groups

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Langerhans Cell Histiocytosis

Key Points

- LCH is a rare multi-system disorder with a wide range of clinical presentations such as skin rash, bony lesions, hormone deficiencies or vital organ involvement.
- The course of the disease is unpredictable, varying from spontaneous regression and resolution to rapid progression and death, or repeated recurrence with risk of irreversible long-term disabilities.
- Delay in diagnosis often limits access to appropriate treatment. Some cases may also be misdiagnosed.
- Treatment may involve conservative surgery, steroid treatment or chemotherapy and in extreme cases bone marrow transplant.

Background

Langerhans Cell Histiocytosis (which includes Hand-Schuller-Christian disease, Letter-Siwe disease and eosinophilic granuloma) is a disease which may present in a variety of ways from a spontaneously regressing single bone lesion to a multi-system life-threatening disorder. It is characterised by the accumulation and proliferation of cells with the characteristics of epidermal Langerhans cells together with other immune cells in various parts of the body[1]. Langerhans cells are normally found only in the skin, lymph nodes, and main airways. However, LCH commonly affects skin (rash) (Figures 5 and 6), bone (single or multiple lesions) (Figure 7), the pituitary gland (diabetes insipidus) (Figure 8) and may also affect the lungs, intestines, spleen, bone marrow, liver and central nervous system (Figure 9). It is more common in children than adults and tends to be more severe in very young children, especially when several organs are affected[2]. Not all children require specific treatment; for others conservative surgery or chemotherapy may be required. Around 10-20% of patients, usually infants, die. In other patients the disease usually burns itself out. However, there may be long-term sequelae due to damage caused by the disease process[3]. Those most frequently reported are orthopaedic problems, hearing loss and neurological consequences and quality of life of survivors is often poor.

The cause of LCH is unknown. It does not result from a known infection and is not a cancer and, although there may be a more than one patient in some (though rare) families, it is usually not hereditary. It may be triggered by an unusual immune reaction to something found in the environment but there is no particular evidence for this.

It is estimated that one in 200,000 children are affected each year. Over 75% of cases occur before the age of 10 years and there are some congenital cases. However, epidemiological data are sparse and only one national incidence estimate (5.4 per million per year) has been reported for Denmark, during the 1980's.

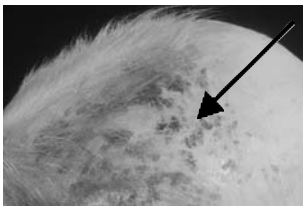

Figure 5: Scalp rash, resembling seborrhoeic dermatitis

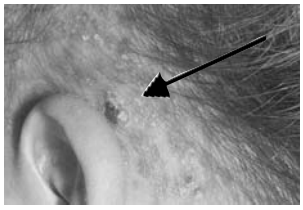

Figure 6: Post-auricular rash

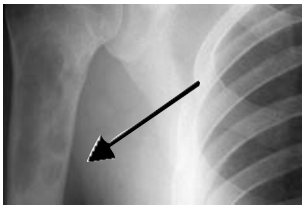

Figure 7: Lytic lesion of the humerus

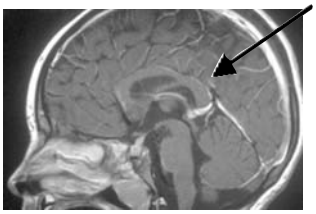

Figure 8: MRI showing pituitary involvement

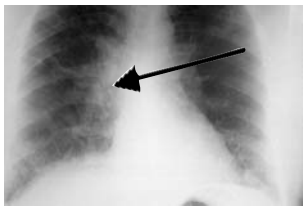

Figure 9: Interstitial shadowing in the acute phase of LCH

Delay in diagnosis often limits access to appropriate treatment. Some cases may also be misdiagnosed.

Objectives

The aims of the study are to

- describe the epidemiology of LCH in the UK and Ireland.

In particular, to

- describe the incidence of LCH in boys and girls by age and extent of disease at diagnosis.
- describe the variation between ethnic groups and assess the frequency of familial LCH.
- describe regional differences in incidence rate assessing geographic variation, eg north/south or urban/rural.
- document patterns of presentation particularly the interval between the onset of symptoms and diagnosis.

Surveillance Period

June 2003 - June 2005 (inclusive).

Methodology

Case Definition

The study includes children of any age 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. Clinicians are encouraged to send slides for review to the study team histopathologist.

(b) Lytic bone lesion or pituitary/hypothalamic abnormality with the characteristics of LCH but not biopsied whether

1. because clinical features suggest spontaneous resolution or
2. because the risk of the biopsy procedure in view of the location of the lesion (eg cervical vertebra, pituitary mass), is considered too great

Clinical features of LCH include: otherwise unexplained bone pain with/without overlying soft tissue swelling, especially in the skull and jaws (floating teeth); proptosis; recurrent otitis with otorrhoea; maculo-papular rash resembling seborrhoeic dermatitis and in the same distribution (especially scalp and flexures) but resistant to topical treatments; interstitial pneumonitis; unexplained colitis; sclerosing cholangitis; diabetes insipidus; unexplained hypothalamic-pituitary dysfunction.

Paediatricians are asked to report cases monthly via the BPSU orange card. For queries regarding diagnosis, please contact Dr V Nanduri or Dr K Windebank.

Alternative data sources

The disease takes many forms and clinicians who are not paediatricians or members of the RCPCH may see patients. Therefore cases are also being sought via a six-monthly mailing by the study team at Newcastle (NCL) to other clinicians including pathologists, oncologists, dermatologists, radiologists, endocrinologists, neurologists, rheumatologists and orthopaedic and paediatric surgeons. A third source of ascertainment has been the United Kingdom Children's Cancer Study Group (UKCCSG), which registers cases of LCH. Questionnaires have been mailed to all clinicians reporting cases to obtain further details. Follow up questionnaires are being mailed one year after diagnosis.

Number of cases expected

Given that the population of children in the UK and Republic of Ireland aged less than 16 years is approximately 12,600,510[6,7], using the incidence rate for Denmark given above, we anticipated that approximately 68 cases would be notified per year.

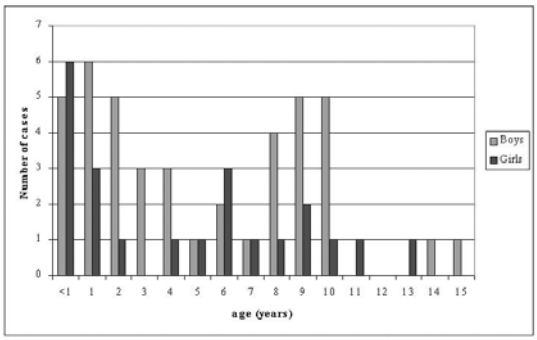

Figure 10: Age of cases at diagnosis

Analysis

Interim results up to April 2005 are reported as there will be a further three months of BPSU surveillance and another six-month mailing by the Newcastle team. In addition, the return of over 50 questionnaires is awaited. Data is therefore incomplete.

There have been 65 confirmed cases to date. There are 43 boys and 22 girls (ratio 1.95:1). There are six children of mixed race, one Philipino and one Turkish child. Two children were diagnosed postmortem. The average age at diagnosis of the remaining cases was 5.2 years (range 0.2-15.1 years). Children presented with varying symptoms: 17 had swellings or lumps, four had rashes or skin lesions, 23 had pain or reduced movement, five had ear discharge, one had lymph node enlargement, 14 cases had more than one symptom. One case was found incidentally following a skull X-ray.

Discussion

There were 65 confirmed cases of LCH found through this study compared with 59 cases of LCH which have been registered with the UKCCSG during the study period to March 2005. The UKCCSG has details of 90-95% of all UK and Irish childhood cancers and the average number of cases per year registered in the 10 years prior to the start of this study was 37. Given that the UKCCSG may not provide the full numbers of LCH cases and has also registered 10 cases which are unknown to us, further cases are expected. The number of outstanding questionnaires, which are being pursued, also indicates this. Further analysis of the questionnaires is still ongoing.

Funding

The Histiocytosis Research Trust sponsors the study.

Ethics Approval

This study has been approved by the London MREC.

Support Group

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Medium chain acyl CoA dehydrogenase deficiency (MCADD)

Key Points

- Medium chain acyl CoA dehydrogenase deficiency (MCADD) is a recessively inherited metabolic disorder that may cause hypoglycaemia, acute encephalopathy and sudden death. It is estimated that, of those presenting clinically, up to one quarter will die at first clinical presentation, with one third of survivors sustaining significant neurological damage[1].
- The Department of Health and the National Screening Committee have funded a pilot newborn screening service for MCADD. Screening commenced in March 2004, and is being carried out over two years in six laboratories covering at least half of all UK births each year.
- The study will obtain estimates of the false negative rate of screening for MCADD. It will also determine clinical outcomes in affected children identified through screening and compare these with similar outcomes in clinically diagnosed children. Surveillance through the BPSU is critical to both of these objectives.

Background

Medium chain acyl CoA dehydrogenase deficiency (MCADD) is a recessively inherited metabolic disorder, which has been identified as a candidate for newborn screening through three systematic reviews commissioned by the Health Technology Assessment Programme[2,3,4]. The reviews concluded that more information was needed on test performance and clinical outcomes in a UK setting. Subsequently the Department of Health and the National Screening Committee have funded a pilot newborn screening service for MCADD. They have also commissioned a concurrent research study to evaluate the service.

Although primary studies of MCADD screening in other countries have been carried out[5,6,7,8,9], important questions remain unanswered[10]. Specifically uncertainty remains over the clinical outcome following detection through newborn screening. Furthermore, the findings of these studies may not be generalisable to UK costs and service provision. In particular, in the UK screening is carried out several days later than in other countries and this may alter test sensitivity and specificity. It is therefore vital to ensure that performance and longer term clinical outcomes of screening are carefully evaluated in a UK setting.

Pilot screening is being delivered from six laboratories in England that are already using tandem mass spectrometry to screen for phenylketonuria and which together screen half the UK's births per annum. Screening started in March 2004, and will continue for 24 months. The concurrent research study will cover a five year period to allow complete follow up to two years of age of affected children. It will obtain the prevalence of MCADD ascertained through screening, as well as the false negative rate of the test. It will also determine clinical and psychosocial outcomes in affected children identified through screening and compare them with those of clinically diagnosed children.

Objectives

Primary: To ascertain all cases of MCADD diagnosed during the study period in order to determine clinical outcome to two years of age with the aim of informing future national screening policy.

Secondary: To determine the detection rate of screening for MCADD in a UK setting.

Surveillance Period

June 2004 - June 2006 (inclusive).

Methodology

Case definition

MCADD is an inherited fatty acid oxidation disorder, resulting from the lack of an enzyme required to convert fat stores into energy. During an intercurrent illness, particularly gastroenteritis, there may be progressive encephalopathy with drowsiness, lethargy and hypotonia progressing to coma. Severely ill children may be hypoglycaemic.

Without screening, children with MCADD usually present clinically before the age of two. MCADD is recessively inherited and between 1 in 40 and 1 in 80 of the UK population are unaffected carriers. It is predicted that the birth prevalence is about 1 in 10,000[1].

Treatment entails avoidance of fasting, use of an emergency dietary regime during intercurrent illness and admission to hospital for intravenous glucose if this is not tolerated.

The diagnosis of MCADD can be made through clinical presentation, through investigation of children with an affected family member, through newborn screening or post mortem investigation.

Diagnosis of MCADD will be accepted if one or more of the following criteria are met:

- Elevated octanoyl carnitine in the presence of normal free carnitine levels on blood test using tandem mass spectrometry
- Characteristic urine profile of organic acids with hexanoyl, suberyl and phenylpropionyl glycine
- Molecular genetic studies confirming presence of the common mutation G985A on one or both alleles
- Enzyme studies based on skin fibroblasts showing reduced activity of MCAD.

The BPSU reporting instructions were modified for the November 2004 mailing, following the publication of 'Sudden Unexpected Death in Infancy: The report of a working group convened by The Royal College of Pathologists and The Royal College of Paediatrics and Child Health'11. The case definition above is broader and simpler than the previous instructions, and it emphasizes the importance of also reporting post mortem diagnoses to the BPSU.

Number of cases expected per year at outset of the study: approximately 65 cases expected.

Denominator source: the total number of births in the UK over the study period.

Alternative data sources: a Biochemical Surveillance Scheme for MCADD (BioSS-MCADD) has been set up through UK laboratories providing diagnostic testing for MCADD, in order to increase ascertainment of cases; detecting those missed by both screening and BPSU reporting. It will also assess the quality of data and completeness of ascertainment of cases. Cases are also notified to the study through the six newborn screening laboratories undertaking MCADD screening.

Analysis

Over the period of the study the following will be reported:

- Prevalence of MCADD in screened and unscreened areas of the UK
- Age and clinical manifestation at diagnosis
- Clinical outcome at two years post diagnosis
- False negative rate of newborn screening for MCADD in screened areas

Numbers of confirmed cases: 45 cases of MCADD have been confirmed through the BPSU during the first 12 months of the study (April 2004 to March 2005), of which 29 were also notified through newborn screening laboratories.

Number of cases by source of data: The three sources of data are:

- British Paediatric Surveillance Unit
- Newborn screening laboratories currently undertaking MCADD screening, which notify screened cases
- Biochemical Surveillance System for MCADD (BioSS - MCADD) - not shown in Figure 1 as surveillance began in March 2005.

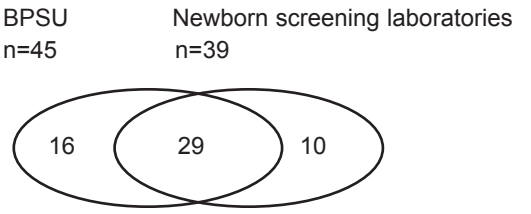

Figure 11: Number of confirmed cases by source of data

Seventy-nine notifications have been received through the BPSU in total. Of these, 45 were confirmed cases of MCADD, three were old cases (diagnosed before April 2004), 13 were duplicates, three were errors, and 15 are as yet unknown, pending return of follow-up questionnaires.

Conclusions

As the first year of surveillance draws to a close, we are very pleased to have received 79 notifications. We would like to encourage clinicians to continue to report any new cases of MCADD, particularly those which present clinically or have been diagnosed at post mortem. We will provide more updates of the study's progress through further BPSU reports and plan to publish interim results in 2006.

Funding

The Department of Health and the National Screening Committee.

Ethics Approval

The London GOS MREC approved the study.

Support Group

Children Living with Inherited Metabolic Disease (CLIMB). Climb Building, 176 Nantwich Road, Crewe, CW2 6BG, Tel: 0800 652 3181. Website: http://www.climb.org.uk/Climb

Acknowledgements

Anne Green, Consultant Clinical Chemist at Birmingham Children's Hospital and Jim Bonham, Consultant Clinical Chemist at Sheffield Children's Hospital for their help in establishing the Biochemical Surveillance Scheme for MCADD. We would also like to thank John Walter, Consultant Paediatrician, at the Royal Manchester Children's Hospital and Tim Cole, Professor of Statistics at the Institute of Child Health and Anne Green for their advice in revising the case definition. We also thank all members of the UKCSNS-MCADD.

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Neonatal herpes simplex virus (HSV) infection

Key Points

- In the first year of surveillance in 2004, twenty infants were reported with confirmed neonatal HSV through the BPSU. A further three confirmed cases were reported directly to the study investigators.
- Virus was typed in all but one case: 10 were HSV-1 and 12 HSV-2.
- Sixteen (70%) confirmed cases were born before 37 weeks gestation. Five (22%), including four premature infants, are known to have died.
- Maternal infection was not diagnosed prior to delivery in any case and 40% of mothers were under the age of 21 years at delivery.

Background

Surveillance of neonatal HSV was previously undertaken through the BPSU in 1986-91[1]. The estimated incidence of infection then was 1.65/100 000 (95% CI 1.3-2.0/100,000). HSV-1 and HSV-2 were reported in equal proportions, although a third of cases were not typed. Changes in the prevalence and type of HSV infection in the last 15 years, together with improvements in diagnostic techniques[2] may have had an impact on the reported incidence of neonatal infection.

Objectives

The aim of the study is to

- estimate the current birth incidence of neonatal herpes infection in the British Isles, and to distinguish the proportion attributable to HSV-1 and HSV-2.
- explore the presentation of neonatal infection, and management of diagnosed cases.
- assess subsequent morbidity and mortality through the notifying paediatrician.
- compare findings with the 1986-91 BPSU cohort, and with other INOPSU studies of HSV.
- inform the debate on antenatal screening.

Surveillance Period

January 2004 - December 2006 (inclusive).

Methodology

Case definition

1) Any infant under one month of age

   (a) with a diagnosis of HSV infection based on virus detection by culture, PCR or IF, or serology - IgM and/or seroconversion, or

   (b) treated with antiviral drugs for suspected HSV infection

2) Any stillborn infant in whom HSV infection is suspected.

Reported cases will be classified as confirmed on the basis of

   (a) virus detection by culture, PCR or IF, or serology - IgM and/or seroconversion, or

   (b) typical clinical manifestations with maternal infection confirmed by either seroconversion during pregnancy or virus isolation around the time of delivery.

Reported cases will be classified as suspected in the absence of laboratory confirmation if the infant has typical clinical manifestations and has been treated with antiviral drugs.

Analysis

Number of reports: By the end of December 2004 there had been 61 reports through the BPSU, of which 20 were confirmed and seven were suspected cases of neonatal HSV infection. Seven reports were still being investigated, 13 were duplicates and 14 were reporting errors (including five infants who were initially treated for HSV, but had no typical clinical manifestations). A further three confirmed cases were reported directly to the study investigators.

Confirmed and suspected cases: Table 10 (overleaf) shows type of infection (localised to the skin, eye and/or mucosa (SEM), disseminated and/or CNS infection, with or without SEM involvement) by case classification and virus type. Virus was typed in all but one confirmed case: 10 (45%) were HSV-1, 12 (55%) HSV-2.

Among the 23 infants with confirmed infection, 40% were born to young mothers (under 21 years at delivery). Sixteen of the 23 infants (70%) were premature: 13 born at 32-36 weeks gestation; and three at less than 32 weeks. In no case was a woman diagnosed with genital herpes infection before symptoms in her infant were noted. There were no reports of hospital acquired infection.

Follow up

Summary follow-up information is being sought at one and three years after birth.

Discussion

There have been more cases reported in the first year of this study than in any single year in the previous study period, but it is too early to tell if this represents a significant increase in incidence[1]. Virus type is available for almost all cases in the current surveillance study. In terms of the nature of infection and the absence of a maternal history of genital herpes the 2004 findings are similar to the previous BPSU study. Data collection continues, and we have already started seeking follow-up information on outcome at 12 months for infants reported in the first half of 2004.

Funding

The National Screening Committee is providing funding to keep neonatal HSV on the orange card. Other costs are being met by the Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, London.

Ethics Approval

The London Multicentre Research Ethics Committee approved the study.

Acknowledgements

We are very grateful to the BPSU and all members of the RCPCH, particularly those paediatricians who have reported cases and completed questionnaires, for their continued support.

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Table 10: Type of infection by case classification and HSV type

	Confirmed infections			Suspected infections	Total confirmed & suspected cases
Type of infection	**HSV-1**	**HSV-2**	**Not typed**		
Skin, Eye, Mucosa (SEM)	4	2	0	5	11
Disseminated and/or CNS infection with SEM	4	7	0	0	11
Disseminated and/or CNS infection without SEM	2	3	1	2	8
Total	**10**	**12**	**1**	**7**	**30**

Non-type 1 Diabetes

Key Points

- Surveillance was initiated in October 2004 to identify the incidence of non-type 1 diabetes in 0-16 year olds.
- During the first six months of surveillance 74 cases of non 1 type diabetes have been reported; these include cases of type 2, non-type 1 secondary to another condition and syndromic type 2 diabetes.
- Case reports have come from diabetic nurse specialists as well as paediatricians.
- Details of cases are being analysed to establish the incidence of obesity-related type 2 and how non-type 1 diabetes is being diagnosed and managed.

Background

The recent epidemic of childhood obesity has led to concerns for children's health. Type 2 diabetes is linked with obesity in adults and up to 85% of children with type 2 diabetes are either obese or overweight at diagnosis. Although the early reports of type 2 diabetes in children were in specific ethnic populations[1, 2], four cases have now been reported in obese white adolescents in the UK[3]. The group reporting this finding have now identified more than ten cases from their single large, diabetes clinic and a national survey of UK paediatric endocrinologists in 2000 identified 25 cases in under 16's; a UK prevalence of 0.21:100,000 although ascertainment was not complete[4]. If, as in the USA, the increasing incidence of childhood obesity in the UK is associated with an increase in the prevalence of type 2 diabetes[5] then there is likely to be a significant impact on health service resources.

As the number of children with type 2 diabetes rises it becomes increasingly important to classify diabetes correctly into types 1 and 2 as the appropriate treatment is often different. Although children with type 1 diabetes often present with an acute illness, such as diabetic ketoacidosis (DKA) while type 2 diabetes has a slower, more insidious onset, the clinical presentation of children with type 2 diabetes may be indistinguishable from type 1. Certain clinical features are highly suggestive of type 2 diabetes, including obesity, a family history of type 2 diabetes, acanthosis nigricans and polycystic ovarian syndrome. The presence of antibodies to glutamic acid decarboxylase-65 (GAD-65), tyrosine phosphatase (IA-2a), and islet cells (ICA) can confirm autoimmune diabetes in children where there is diagnostic doubt and the absence of autoantibodies in children with obesity-related diabetes strongly suggests type 2 diabetes. However, 10% of children with type 2 diabetes also have a positive antibody test.

This survey will explore the early clinical features of type 2 diabetes and its association with obesity. The follow-up questionnaire at one year, identifying clinical management, will help to confirm how many non-type 1 cases are type 2 and will also examine short-term morbidity.

Surveillance Period

October 2004 - October 2005 (inclusive).

Objectives

The study aims to address

- the UK and Ireland incidence of all non-type 1 diabetes in children 0 - 16 years.
- the relative incidence of obesity-related type 2 diabetes, familial type 2 diabetes and other syndromic diabetes.
- the clinical features at presentation for the different types of non-type 1 diabetes.
- the features that distinguish type 2 diabetes from syndromic and type 1 diabetes.
- the way non-type 1 diabetes is being diagnosed and treated by paediatricians.
- the short-term (one year after diagnosis) morbidity associated with non-type 1 diabetes.

Methodology

Paediatricians are asked on a monthly basis to report all cases meeting the case definition, through the orange card system. Around 150 diabetes nurse specialists (DNS) have been identified as additional sources of cases and have also been asked to report cases every two months. Paediatricians reporting a case are sent a questionnaire seeking demographic details and clinical features. For all valid cases, a second questionnaire will be sent to the reporting paediatrician one year after the case was first reported. On completion of the surveillance

period, we will determine the incidence and presenting patterns of the various forms of non-type 1 diabetes (NT1D), as well as establishing management patterns and any associated morbidity.

Case Definition

Surveillance definition: Any new diagnosis of non-type 1 diabetes (suspected or confirmed) in a patient 0–16 years of age i.e. up to but not including their 17th birthday. These may not be new cases of diabetes, but newly recognised as atypical for type 1.

Clinical features suggestive of non-type 1 diabetes are:

- Diabetic but low (<0.5 units/kg per day) insulin requirement, outside of the honeymoon period (usually by 3 years after diagnosis).
- Diabetic but no insulin requirement.
- Suspiciously good control on insulin (i.e. HbA1c within normal range for non-diabetics, few hyperglycaemic episodes, absence of ketonuria).
- Acanthosis nigricans.
- Diabetes as part of a recognised syndrome (e.g. Wolfram/DIDMOAD, diabetes and deafness, Down syndrome, Prader Willi syndrome).
- Diabetes secondary to another condition (e.g. cystic fibrosis, bone marrow transplant, thalassaemia).

Other features suggestive of non-type 1 diabetes include:

- Obese patient.
- Family history of type 2 diabetes.

Analysis

During the first six months of the study 199 cases have been reported in total. 133 (67%) of these cases were notified by paediatricians and 66 (33%) were notified by DNSs. So far 141 questionnaires have been returned giving a 71% return rate.

74/199 (37%) cases have been confirmed as meeting the American Diabetic Association criteria for diabetes and having NT1D. Figure 12 shows the classifications used in this study for the different types of non-type 1 diabetes. A distribution of the different types of non-type 1 diabetes reported to date is shown in Figure 13. Of 74 confirmed cases, 56 (76%) were notified exclusively by paediatricians and 12 (16%) were notified exclusively by Diabetic Nurse Specialists (DNSs). Six cases were reported by both paediatricians and DNSs.

Of the 74 cases, 40 were female and 34 were male. Type 2 diabetes is the most commonly reported NT1D with 38/71 (54%) cases. Diabetes secondary to another condition made up 15/74 (21%) of reported cases. Of these, nine cases were diabetes secondary to cystic fibrosis. Other diagnoses included steroid-induced diabetes and diabetes as a result of bone marrow transplantation.

9/74 (12%) cases of Maturity Onset of the Young (MODY) were reported. The genetic mutations most commonly reported were in the Glucokinase gene. 6/74 (8%) cases were syndromic diabetes, and 5/74 (7%) cases were diabetes secondary to an unrecognised syndrome. Cases of diabetes as part of a known or suspected syndrome were reported, including Alstroms syndrome (1), Turner's syndrome (1) and transient neonatal diabetes (4). There was one case in which the category of NT1D was not known.

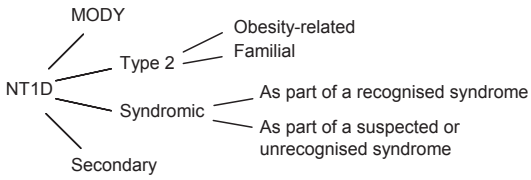

Figure 12: Classification of NT1D

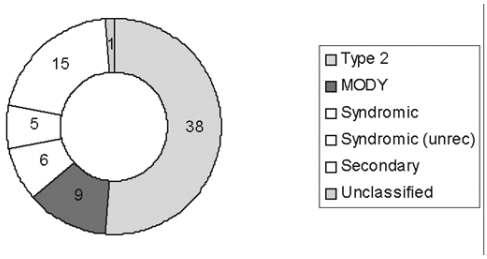

Figure 13: Types of NT1D reported (October 04-April 05)

Further analysis of the clinical data is ongoing and a full report will be available at completion of the study. In this study, diabetic nurses appear to have reported additional cases not reported by the paediatricians. However, as diabetic nurses and paediatricians often work in teams, it is likely that the reporting sources are not independent and joint reporting may occur. For this reason, capture-recapture analysis will not be used in this study[6].

Funding

The study is partly funded by the Diabetes UK small grant scheme.

Ethics Approval

The South West MREC approved this study in September 2004.

Support Group

Diabetes UK, from whom patient information is available on request, can be contacted at 10 Parkway, London NW1 7AA. Tel: 020 7424 1000. Web: http://www.diabetes.org.uk

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Progressive Intellectual and Neurological Deterioration In Children (PIND)

Key Points

- Further active surveillance is planned until April 2006.
- Variant Creutzfeldt-Jakob disease (vCJD) has not gone away, although paediatric cases have not appeared since 2001. Adult cases are still presenting and a case report last year raised concern that vCJD may be transmitted by blood transfusion[1]. In addition a case of preclinical vCJD was reported in a male who had received blood from a donor who later developed vCJD[2]. At autopsy the recipient was found to have protease-resistant prion protein in his spleen and in a cervical lymph node, but not in his brain. There was particular concern because genotyping showed that the recipient was a methionine/valine heterozygote at codon 129 of the prion protein gene on chromosome 20. Previously all confirmed cases of vCJD have been methionine homozygous. This raises the possibility that methionine/valine genotypes might develop vCJD with a longer incubation period and that they will present in the future, emphasising the need for continuing surveillance.
- Even if you have made a diagnosis we still want to hear about all children with progressive intellectual and neurological deterioration (PIND). This is important because we want to ensure that ascertainment is as complete as possible by discussing the anonymised case details with the Expert Group of paediatric neurologists who review all PIND cases.
- Six cases of vCJD have been reported to the study since December 1998. Of these four have been classified as "definite" and two "probable" according to the National Creutzfeldt-Jakob Disease Surveillance Unit. All six cases have died.
- After almost eight years of surveillance 1866 children have been notified. The Expert Group of six paediatric neurologists has discussed 1326 cases. 773 have a definite diagnosis which is not vCJD, and these comprise 114 known degenerative conditions.
- There are districts that report relatively large numbers of PIND cases. In some of these areas there are high consanguinity rates and a heterogeneous mixture of diagnoses[3].

Background

Active prospective surveillance of UK children with progressive intellectual and neurological deterioration (PIND) commenced in May 1997. Funded by the Department of Health, it is being carried out via the BPSU in conjunction with the National Creutzfeldt-Jakob Disease Surveillance Unit in Edinburgh (NCJDSU) and the Health Protection Agency (HPA).

The main aim is to determine whether or not any children in the PIND group have developed variant Creutzfeldt-Jakob disease (vCJD)[4]. vCJD has been described in patients as young as 12 years of age[5] and it could occur in younger children. It is possible that the clinical presentation of vCJD in young children might be different from that described in adults. The strategy is to detect suspected vCJD cases by looking at a broader group of conditions causing PIND in children. It is only by carefully examining the clinical details in all these PIND cases that we can be reasonably sure that vCJD is not being missed among the many rare neurodegenerative disorders that affect children. An Expert Group of six paediatric neurologists independently reviews the anonymised clinical details for all the PIND cases. In this way, not only is there the opportunity to detect vCJD cases, but also unique epidemiological data on a variety of PIND conditions are obtained[6].

The surveillance team use a detailed questionnaire to gather information via a telephone interview or site visit to review the case notes; alternatively the notifying paediatrician may wish to complete the questionnaire. There is further follow up of undiagnosed cases via the local paediatricians.

Objectives

- To carry out active prospective surveillance of UK children with paediatric neurological conditions (including those with specific diagnoses) defined by their common presentation - PIND - to determine the incidence and distribution of PIND.

- To evaluate cases presenting with PIND in order to classify them and investigate the possibility that vCJD is occurring in children.

Surveillance Period

Surveillance commenced in May 1997 and continues.

Methodology

Case definition

Paediatricians are asked to report monthly any child under 16 years of age at onset of symptoms who fulfils all of the following three criteria:

- Progressive deterioration for more than three months

  with

- loss of already attained intellectual/developmental abilities

  and

- development of abnormal neurological signs.

Excluding:

- Static intellectual loss, e.g. after encephalitis, head injury or near drowning.

Including:

- Children who meet the case definition even if specific neurological diagnoses have been made.
- Metabolic disorders leading to neurological deterioration.
- Seizure disorders if associated with progressive deterioration.
- Children that have been diagnosed as having neurodegenerative conditions but who have not yet developed symptoms.

Reports restricted to: Cases seen in the last month but including those whose conditions began earlier (i.e. including "old cases" of children in follow-up (if seen in that month).

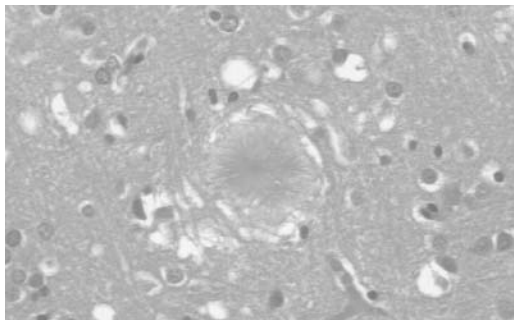

Figure 14: Florid Plaque in vCJD x400 - haematoxylin/eosin stain

Analysis

By the end of February 2005 a total of 1866 children had been reported via the BPSU (see Figure 15). There were 773 PIND children with a definite underlying diagnosis, 97 in whom no diagnosis had been made and 159 who were still under investigation. There were 731 "No Cases" including those who did not fulfil the criteria for PIND, reporting errors, duplicate notifications etc. The 100 outstanding cases include 5 due for discussion at the April 2005 Expert Group meeting and 95 awaiting data collection. The six cases of definite/probable vCJD are discussed below.

Definitive or probably cases of vCJD: Six cases of vCJD have been notified - the youngest was a girl aged 12 years at onset. There were three other girls and two boys. One child was notified in 1998, two in 1999, one in 2000 and two in 2001. All have since died and neuropathology has confirmed vCJD in four of them (classified as "definite" cases). Two have died without neuropathological study (classified by the NCJDSU criteria as "probable" cases[5], Figure 14).

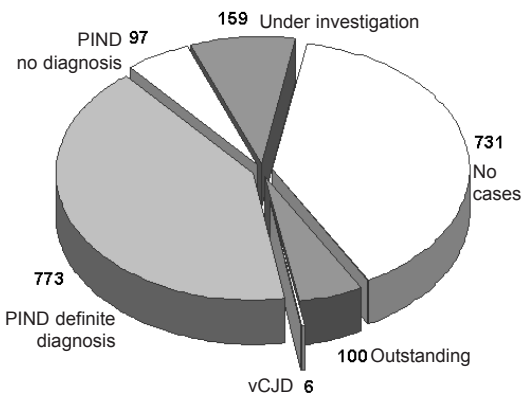

Figure 15: PIND study - current status

Children who have definite PIND diagnoses other than vCJD: The study is producing unique population-based data on the causes of PIND. The majority of reported children with PIND have a known degenerative diagnosis or a likely underlying diagnosis that is not vCJD. In the 773 children with a confirmed diagnosis other than vCJD there were 114 different neurodegenerative conditions. The eight most commonly occurring diagnoses are shown in Figure 16.

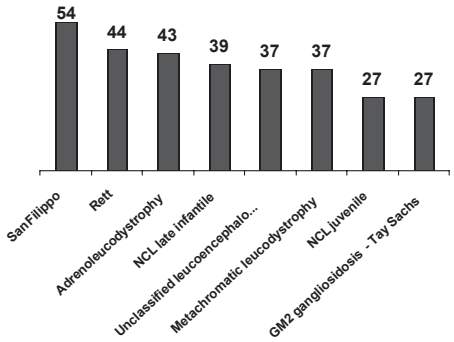

Figure 16: Eight most commonly reported PIND diagnoses

Variation in reporting by district: Geographical analysis by hospital of report and by residence reveals significant variations. A few hospitals have not reported any cases. There are some areas with considerably higher numbers of children with PIND. Yorkshire remains the highest reporting BPSU region (226 cases) with North East Thames (206 cases) followed by West Midlands (203 cases).

Variation in reporting by category of referring paediatrician: General paediatricians notified the largest number of children followed by paediatric neurologists then community paediatricians (Figure 17).

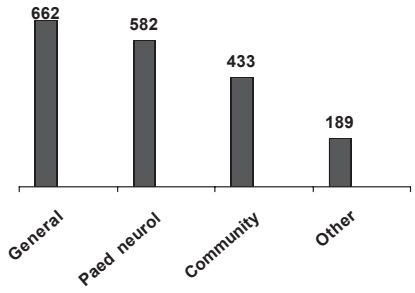

Figure 17: Category of referring paediatrician

Interim conclusions

PIND surveillance has been running for almost eight years now. Six cases of vCJD in children under 16 years of age at first presentation have been notified to the study. There were four cases of definite vCJD and two cases of probable vCJD. One girl was aged 12 years at onset, the youngest ever reported case of vCJD. There have been no other children with the clinical features of vCJD, however there is concern that more childhood cases may appear. Eight years is a short time to perform surveillance for a disease about which there are still many unanswered questions - for example, the number of children who may be incubating vCJD, the length of the incubation period and the exact nature of transmission. New cases are still appearing in older patients and there is now concern about possible transmission of vCJD by blood products.

Funding

This study is funded by the Department of Health.

Ethics Approval

Approval was given in 1997 by the Local Research Ethics Committee, Addenbrooke's Hospital and the then Public Health Laboratory Service Ethics Committee.

Acknowledgements

PIND surveillance is working very well and is yielding valuable information about the conditions that lead to PIND in children. Many thanks to the UK paediatricians who are still responding enthusiastically. The PIND surveillance team is very grateful to the members of the paediatric neurology Expert Group (Prof J. Aicardi, Dr P. Baxter, Dr S. Green, Prof. R. Robinson, Prof. R. Surtees and Dr J. Wilson) for all their work in classifying cases.

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Severe hyperbilirubinaemia in the newborn

Key Points

- For the period May 2003 - March 2005 86 cases were confirmed.
- Incidence rate on the first years data was 0.05 per 1,000 (CI 0.03 - 0.07).
- Two children died.
- Early discharge from maternity unit, breast-feeding, ethnic minority origin and co-morbidity such as haemolysis and sepsis appear to be important associations with severe jaundice.

Background

During the 1990's, bilirubin encephalopathy was reported with increasing frequency in term neonates in North America[1] and Europe[2]. Previously, in the developed world, this condition was encountered primarily in infants with severe Rhesus isoimmunisation, and it had virtually disappeared thanks to developments in preventing and treating Rhesus disease. The apparent reappearance of severe neonatal jaundice and bilirubin encephalopathy were ascribed to increasingly early discharge of mothers and infants from the maternity unit, and to a less aggressive approach to investigation and treatment of neonatal jaundice[1,3]. Similar trends in the management of newborns have occurred in the UK, but there has been no recent comprehensive study of the national incidence of severe neonatal jaundice.

Objectives

Primary: To determine the incidence of severe neonatal hyperbilirubinaemia in the United Kingdom and Ireland.

Secondary:

- To identify clinical and demographic variables associated with severe neonatal jaundice.
- To identify possible consequences of the occurrence of severe neonatal jaundice, such as the need for exchange transfusion, the occurrence of bilirubin encephalopathy, and associated morbidity and mortality.

Surveillance Period

May 2003 - May 2005 (inclusive).

Methodology

Paediatricians are asked to report cases meeting the above definition via the BPSU orange card scheme. Those who notify cases are sent a questionnaire requesting clinical and demographic information, including ethnic origin, gestational age, birth weight, mode of feeding, age at discharge from the maternity unit, first and peak serum bilirubin concentrations, associated symptoms, co-morbidity and short term outcome. A brief questionnaire is sent after

12 months requesting simple information about general health, developmental progress and hearing.

Surveillance was extended to a second year in order to gather more data on bilirubin encephalopathy.

The anticipated number of cases at the study outset, extrapolating from the Ontario experience[4] was 300 per year.

Case definition

Unconjugated serum bilirubin (SBR) >510 micromol/L in the first month of life.

Analysis

Up to March 2005, 154 cases had been notified to the BPSU, to date of these 86 had been confirmed. Thirty-eight cases were confirmed in the first 12 months of surveillance.

Confirmed cases:

Incidence: Taking the denominator as live births (742,069) the calculated incidence during the first year of surveillance in the UK (there were no cases from Ireland) was 0.05 per 1,000 (CI 0.03 - 0.07). 59% of cases were male and 40% were female, with 1% unknown. The median (range) birthweight was 3.2kg (1.8 - 4.2), and median (range) gestation was 38 (35-42) weeks.

Ethnic origin: Using ONS ethnicity criteria 47% were classified as white, 19% as Asian, 10% as black, 8% as mixed and 16% as other.

Mode of feeding: 80% of infants were breast-fed, 13% had formulae milk only and 6% had a combination of both. Data for 1% was unknown.

Age at initial discharge (days, median, range): 24 to 48 hours (< 24 hours to 18 days). There were two home deliveries.

Maximum unconjugated SBR micromol/L (median, range): 584 (510 - 802).

Age at maximum SBR (days, median, range): 4 (1 - 9).

Treatment: Seventy-one infants were readmitted with jaundice. The median (range) age of those readmitted was 4 (1 - 9) days. Forty infants received a total of 46 exchange transfusions.

Six infants showed clinical features of bilirubin encephalopathy. Two infants died, both had concurrent sepsis.

Table 11: Associated morbidity in reported cases

Associated diagnoses	Infants
Haemolysis	39
Dehydration	23
Marked bruising	5
Sepsis	2
Other	4
None	23

Conclusions

The primary objective of the study, to determine the incidence of severe hyperbilirubinaemia in the newborn, has been attained for the first year of surveillance. At 0.05 per 1,000 live births, the UK incidence appears to be lower than that reported in North America. Using the same bilirubin threshold for case definition, Newman et al reported an incidence of 0.1 per 1,000 live births in a managed care catchment in California between 1995 and 1998[5], and Lee et al reported an incidence of 0.38 per 1,000 in Ontario between 1992 and 1994[4].

Since we do not have comparable information for the denominator data, we cannot describe the following associations as formal risk factors for severe neonatal jaundice. Nonetheless, its apparent association with male gender, early discharge, breast feeding, non-white ethnic origin, relative immaturity and co-morbidity such as haemolysis and sepsis is almost identical to the American experience[1,3].

Paediatricians, midwives and family doctors should be aware that, in most cases, severe neonatal jaundice presents after the mother and infant have been discharged from the maternity unit. Particular vigilance in the first week of life is warranted for non-white infants, relatively immature infants and breast-fed infants, especially if there is difficulty in establishing breast feeding resulting in dehydration.

Ethics Approval

Approved by Metropolitan MREC in March 2003. Approval extended for 1 year in 2004.

Funding

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Support Group

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Symptomatic Toxoplasmosis in Childhood

Key Points

- Confirmed cases of symptomatic toxoplasmosis were reported more often by ophthalmologists than by paediatricians or laboratories.
- Most confirmed cases of symptomatic toxoplasmosis were due to congenital infection.
- Most confirmed cases with ocular toxoplasmosis presented in adolescence and were considered to have postnatally acquired toxoplasmosis.
- Retrieval of Guthrie Card blood spots was feasible but limited by difficulties obtaining parental consent.

Background

The primary aim of the study was to determine birth prevalence of symptomatic congenital toxoplasmosis in order to inform decisions about neonatal screening for congenital toxoplasmosis.

To obtain an accurate estimate of the birth prevalence of symptomatic congenital toxoplasmosis it is important to ascertain children with congenital toxoplasmosis who first present with retinochoroiditis in childhood. Such children need to be distinguished from the much larger number of children who acquire toxoplasma infection postnatally and develop retinochoroiditis[1]. Retinochoroidal lesions due to congenital and postnatally acquired toxoplasmosis are indistinguishable (Figure 18). To differentiate between congenital and postnatal acquired infection, we classified children based on other findings indicative of the timing of infection. Children with probable and definite retinochoroiditis who presented with early childhood signs (eg: history of squint in affected eye, hydrocephalus, or history of cerebral palsy or neurodevelopmental delay from infancy) and serological evidence consistent with maternal or congenital toxoplasma infection were considered to have congenital infection. Children whose first symptoms of retinochoroiditis took place after four years of age and who had no other findings suggestive of maternal or congenital infection were considered to have acquired the disease postnatally. As a result, the study provides information on both the birth prevalence of congenital toxoplasmosis and the incidence of postnatal infection resulting in symptomatic eye disease.

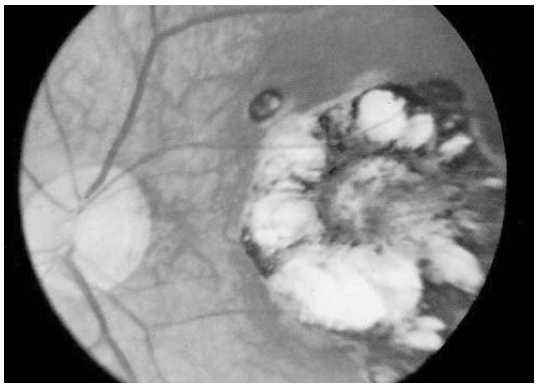

Figure 18: Macular lesion of the eye

Objectives

The study aims to

- determine the birth prevalence of symptomatic congenital toxoplasmosis.
- determine the severity of clinical manifestations and age at first diagnosis in children with symptomatic toxoplasmosis according to whether infection was likely to be congenital or acquired postnatally.
- describe the management of children with suspected symptomatic congenital toxoplasmosis in the British Isles.
- determine the feasibility of testing for specific IgM/IgA antibodies using stored Guthrie card blood samples in children with suspected congenital toxoplasmosis.

Surveillance Period

July 2002 - June 2004 (inclusive).

Methodology

- When a paediatrician reported a suspected case, they were sent a questionnaire for completion and a consent form and information sheet to be forwarded to the parents asking them for permission to recall and test their child's Guthrie card blood spot for toxoplasma specific antibodies. To minimize the workload for ophthalmologists, we only sent the consent form after we had received their questionnaire and confirmed that the child was a probable case and had not already been contacted by a paediatrician. We contacted the relevant neonatal screening laboratory to request a blood spot sample for children whose parents had consented.

Case Definition

- Paediatricians were asked to report any child (<16 years) or stillbirth with suspected congenital toxoplasmosis. This reporting definition included any child: (a) under 2 years with toxoplasma-specific IgM, IgA or IgG antibodies (after this age antibody responses may reflect postnatally acquired infection), or (b) any child with unexplained retinitis; or c) children with hydrocephalus, intracranial calcification, microcephaly, or microphthalmia, or infants with unexplained hepatosplenomegaly and lymphadenopathy.
- Ophthalmologists were asked to report any newly diagnosed child suspected to have congenital toxoplasmosis including any child with unexplained retinochoroiditis or other ocular findings consistent with congenital toxoplasmosis.
- Reference laboratories were asked to report any clinical samples referred for testing that met the above criteria.

Analytic case definition - We classified all children reported during the two-year study period according to their likely congenital infection status and the presence of toxoplasma retinochoroiditis. Classifications were performed independently by two assessors (Dr Ruth Gilbert and Mr Miles Stanford) and discrepancies resolved by discussion. We used the classification developed by Lebech et al[2], together with probabilities derived from published evidence on the risk of mother to child transmission of toxoplasmosis[3], the risk of developing retinochoroiditis in children infected with congenital or postnatal acquired toxoplasmosis[4], the estimated incidence of postnatal acquired and congenital toxoplasmosis in the UK[5-6], and evidence on the risk of fetal loss and intrauterine growth retardation in toxoplasma-infected pregnancies[7]. Children were classified on a four point scale (definite, probable, possible, or not). We included only those classified as definite or probable congenital toxoplasmosis, and/or definite or probable toxoplasma retinochoroiditis in the analyses.

Number of cases expected per year at outset of study - A maximum of 20 confirmed cases per year were expected. Using data from countries with a similar seroprevalence of infection in pregnancy we estimated the expected birth prevalence to be about 1 in 10,000 live births or about 70 births in the UK per year[5]. Of these, up to 10% (seven children) would be expected to die or to present with serious neurological symptoms, squint or serious visual impairment, or acute ocular symptoms, before five years of age (unpublished data from the European Multicentre Study on Congenital Toxoplasmosis). To estimate the number of children expected to present to ophthalmologists, we extrapolated from a previous surveillance study of suspected toxoplasma retinochoroiditis in a population of adults and children of 7.4 milllion[8]. It was estimated that the incidence of newly detected symptomatic ocular toxoplasmosis in children in the UK overall would be approximately half that observed in the regional study (3.7/million/year), due to the different prevalence of high risk ethnic groups in the UK compared to the study population. Using these data we expected about 16 children per year to present to ophthalmologists in the UK.

Denominator source - Live births in England and Wales from 1987 to 2004 was taken as the denominator. Although cases were ascertained from the whole of the British Isles, we restricted the estimate of birth prevalence to England and Wales because of a lack of reports from the Toxoplasma Reference Laboratories in Scotland and Ireland. In addition, few ophthalmologists in Northern Ireland or Ireland reported to the study.

Alternative data sources

The British Ophthalmic Surveillance Unit (BOSU) and five toxoplasma referral laboratories in the UK and Ireland were used as alternative reporting sources. The number of terminations of pregnancy due to hydrocephalus suspected to be due to toxoplasmosis was determined, but there were no further details on these cases.

Analysis

Outline of proposed analysis

1. The number of children reported in the surveillance period in England and Wales and classified as definite or probable congenital toxoplasmosis will be used to determine the birth prevalence of symptomatic congenital toxoplasmosis. To derive an upper estimate, we will perform sensitivity analyses that include all confirmed cases of congenital or postnatal toxoplasmosis.
2. The age at presentation, severity of symptoms, visual impairment, and management will be reported separately for children classified as either definite or probable congenital or postnatally acquired toxoplasma infection.

Interim results

During the 24 months study period from July 2002 to June 2004, 181 reports of suspected toxoplasmosis were received. These reports were evenly distributed among BPSU, BOSU and the reference laboratories (Table 12). Completed questionnaires were received on 122 (67%) of the 181 reports. There were 29 (16%) notification errors and 30 (17%) questionnaires not received.

Table 12: Reports of suspected congenital toxoplasmosis in childhood by reporting source and country

Source of notification	cases notified	questionnaires received
BPSU	41	26
BOSU	69	37
Referral labs*	50	50
Individual**	3	1
Secondary sources***	18	8
Country of notification		
England	150	102
Wales	7	5
Republic of Ireland	6	4
Northern Ireland	7	6
Scotland	11	5
Total	**181**	**122**

* No response from Inverness, or Dublin laboratories.

** Case notification received from individual clinicians seeing child with suspected congenital toxoplasmosis who did not notify the case to the BPSU/BOSU.

*** Questionnaires from secondary sources (could be paediatric, ophthalmic or laboratory) were from clinicians seeing the child but who did not initially notify the case to the surveillance study.

Of the 122 questionnaires received, 17 were duplicates, hence 105 cases were reported. However, only 64 cases had a first presentation within the surveillance period (28 were diagnosed before, one after, and 12 had an unknown date of presentation (none of these were classified as definite or probable cases). Two of the 64 cases diagnosed during the study period were excluded because they were immuno-compromised (both had HIV infection).

Of the 62 cases that met the reporting definition during the surveillance period, only 38 who presented with symptoms or signs relating to definite or probable toxoplasma infection met the case definition. The remaining 24 cases were classified as possible or unlikely toxoplasma infection. Of these, seven (29%) were either miscarriages or still births with serological evidence of maternal infection, but no test results to indicate fetal infection, two (8%) were toxoplasma IgG negative, 10 (42%) were infected in pregnancy but no evidence of postnatal infection, one (4%) was missing child and maternal serological results, and a further four (17%) had retinochoroiditis due to other causes - multifocal choroiditis, toxocara, and intermediate uveitis.

Figure 19 (overleaf) shows the reporting source for the 38 cases that met the case definition. Ophthalmologists reported more cases (19) than paediatricians (4). All eight cases reported by laboratories were reported by the Toxoplasma Reference Laboratory in Swansea.

Table 13 (overleaf) shows the distribution of cases according to congenital and postnatal acquired toxoplasmosis and the presence of ocular disease. A total of 22/38 (58%) cases had serological findings and/or clinical manifestations consistent with congenital toxoplasmosis. Of these, 15/22 (68%) had ocular manifestations, and three presented during school age (at 5, 10 and 11 years). There were 16/38 (42%) children classified as postnatal acquired toxoplasmosis. All presented with retinochoroiditis after the age of four years and 14/16 (88%) of them first presented in adolescence. The type and severity of clinical manifestations and associated visual impairment of toxoplasma infection, as well as the incidence estimates, will be reported in detail elsewhere.

Among the 38 probable cases, 32% (12/38) did not meet the criteria for Guthrie card dried blood spots retrieval: four were born outside the UK; three were non life births; and five were solely identified and reported by reference labs and could not be approached for consent. Twenty six consent forms for the eligible cases were sent to clinicians to be forwarded to parents. Only 15 were forwarded. One was not forwarded because the child failed to attend clinic and was lost to follow up. Reasons for not forwarding the remaining 10 were not given. We received consent forms for 13/15 families approached. All gave permission to recall and test their child's blood spots. At the time of writing, blood spots for 8/13 (61%) children were successfully retrieved, including one for a child born in 1986.

Table 13: Confirmed cases according to classification as congenital or postnatal acquired

	Congenital toxoplasmosis	Postnatally acquired toxoplasmosis	Total confirmed cases
With ocular disease	15	16	31
Without ocular disease	7	0	7
Total confirmed cases	22	16	38

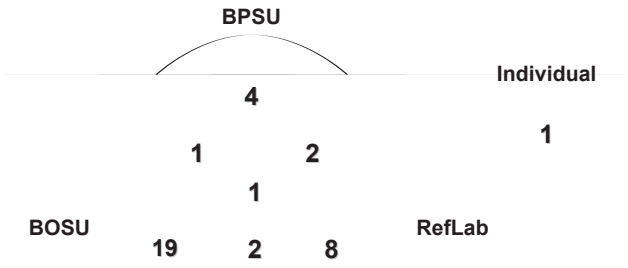

Figure 19: Sources of confirmed cases within the study period (Total 38)

Conclusions

The number of cases of symptomatic toxoplasmosis identified by the study, whether due to congenital or postnatally acquired infection, was similar to that predicted. Confirmed cases of symptomatic toxoplasmosis were reported more often by ophthalmologists than by paediatricians or laboratories, and most had congenital toxoplasmosis. However, most cases with ocular toxoplasmosis were considered to have postnatally acquired toxoplasmosis and presented most frequently in adolescence. Retrieval of Guthrie Card blood spots was feasible but limited by difficulties in contacting parents for consent.

Funding

The British Council for the Prevention of Blindness contributed to the funding of the project.

Ethics Approval

This study was approved by the London Multi-Centre Research Ethics Committee

Acknowledgements

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Support Group

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Tuberculosis (TB) in childhood

Key Points

- Notification rates are 3 per 100,000.
- Children from the Indian subcontinent and Black African children have higher rates of notification than white children.
- Only 26% of cases are culture confirmed.

Background

In the UK tuberculosis (TB) notification rates have stabilised at 11-12 /100 000 population. However, notification rates in London over the past decade are more than three times this level. Immigration from high prevalence countries and an increase in HIV infection have been suggested as possible factors leading to the resurgence in TB cases in some areas of the UK[1]. In particular, notifications of TB in children have increased at a rate greater than the overall TB notification rate. This is most critical in London where there has been a 130% increase[2]. Cases of childhood TB are important from a public health viewpoint. Not only do they form a reservoir of possible future cases but they are also sentinel events reflecting recent transmission from an infected adult who will also be a risk to others[3].

Currently, national data on paediatric TB are derived from statutory notifications and, since 1999, via the enhanced surveillance system. Additional data is available from Mycobnet, a system which allows monitoring of anti-TB drug resistance in the UK, provides information on TB species, and also provides a degree of demographic data. However the accuracy of these parallel reporting systems in determining the true incidence of childhood TB in the UK is uncertain. The completeness and accuracy of the enhanced surveillance system has not been validated, and it has been suggested that both under- and over-notification of cases of childhood TB occurs[4,5]. There is also a lack of data on the clinical spectrum of childhood TB in the UK. Although pulmonary TB remains the most common form of childhood TB disease, there has been an increasing number of children with TB central nervous system disease in London who represent an unusually high proportion of all childhood TB cases. (P.Atkinson, CDSC unpublished data)

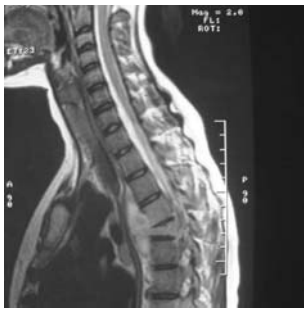

Figure 20: Spinal MRI demonstrating Pott's fracture

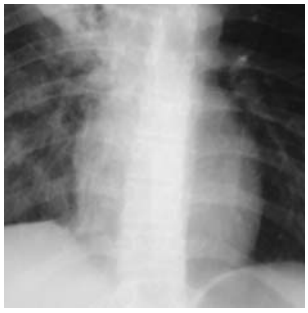

Figure 21: CXR, Miliary TB with associated pneumomediastinum

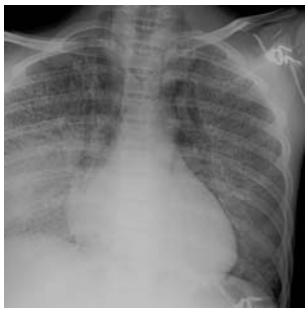

Figure 22: CXR, Cavitary tuberculosis - mainly seen in adolescents or adults

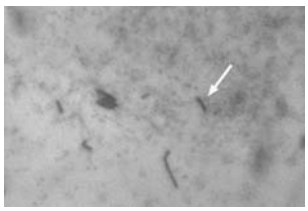

Figure 23: Acid-fast bacilli demonstrated by a Ziehl-Neelson stain

The Chief Medical Officer for England has published a strategy for health protection entitled Getting Ahead of the Curve[6]. In this strategy TB was identified as a key infectious disease problem necessitating intensified control measures including surveillance to reduce illness and death. A TB Action Plan, Stopping TB in England, was published in 2004. This plan highlighted the need for high quality surveillance as local, national and international levels[7]. In addition a children's National Service Framework (NSF) has been proposed to develop networks

Table 14: TB cases by gender and geography

		Geography						
		England not London	London	Northern Ireland	Republic of Ireland	Scotland	Wales	Total
Gender	Male	103	56	3	3	9	4	178
	Female	111	69	2	1	8	7	198
Total		**214 (57)**	**125 (33)**	**5 (1)**	**4 (1)**	**17 (4)**	**11 (3)**	**376 (100)**

Brackets: % of total number of cases

of care for children[8]. It has been proposed that the NSF include an infection strategy which prioritises preventative and clinical services for children with infections[9]. This BPSU study will be important in both validating the current enhanced surveillance system and informing the development of services for children with TB as part of the overall infection strategy for children.

Objectives

The study aims to

- estimate the incidence of TB in children.
- describe the clinical features of TB in children.
- identify how children with TB are identified and where they are managed.
- assess the validity of the Enhanced Surveillance Program for cases of TB in children.

Surveillance Period

December 2003 - January 2005 (inclusive).

Methodology

Case Definition

Paediatricians were asked to report any child less than 16 years of age with newly diagnosed TB.

Cases include:

- *Confirmed cases*: culture-confirmed disease due to Mycobacterium tuberculosis complex infection (M. tuberculosis, M. bovis, M. africanum).
- *Probable cases*: not culture-confirmed but have a clinical/radiological diagnosis of TB and/or are treated with two or more antituberculosis drugs.

Analysis

551 notifications have been received and returns for a further 25 are awaited. To date, data is available for 376 cases, giving an overall rate of 3.0 cases per 100,000 children. This rate is higher in England, 3.5 cases/100,000. Rates are even higher in London, which has 8.7 cases/100,000 children - in contrast to a rate of 2.6 cases/100,000 for England if we exclude London.

One hundred and twenty-five cases (33%) were reported in London and 214 (57%) from the remainder of England (Table 14). There have been cases across all ages with a trend to more cases in the toddler and older age groups (Table 15, Figure 24). Of 368 cases for whom the country of birth was known, 248 (67%) were born in the UK.

Two hundred and eighty-three (73%) cases had respiratory disease, i.e. parenchymal chest X-ray (CXR) changes, pleural disease or hilar lymphadenopapthy, with or without non-respiratory disease. Fifty-three percent of children had been vaccinated with BCG, and in

Table 15: TB cases by age and gender April 05

Age (years)		< 3	4 - 7	8 - 11	12 - 15	Total
No of cases	Male	57	41	38	42	177
	Female	58	38	30	72	196
Total		**115 (30.6)**	**79 (21.0)**	**68 (18.1)**	**114(30.3)**	**376(100)**

For those cases for whom there was data on ethnicity, 123 (33%) were from the Indian subcontinent (ISC), 107 (29%) Black African, and 91 (24%) white. This confirms elevated rates in the ISC and Black African populations (Table 3).

Figure 24: Ages of TB notifications

11% the BCG vaccination status was unknown (Figure 25). Twenty-five children had a diagnosis of meningitis and/or CNS tuberculoma. Nine of these children were vaccinated with BCG, 12 were unvaccinated and in four the BCG status was unknown.

In 245 (64%) cases there was an attempt to confirm the diagnosis with microbiological or histological investigations. Ninety-nine were culture-confirmed (40% of cases in which culture was performed, or 26% of all cases).

Histology was performed in 41 cases and acid-fast bacilli or granulomata were seen in all but 4 of these.

More children (196 cases) received quadruple (rifampicin, isoniazid, pyrazinamide, ethambutol) therapy rather than triple therapy (161 children).

Conclusion

Rates of childhood TB in London are considerably higher than in other areas of the UK and Ireland. Children from the Indian subcontinent and Black African children have much higher rates of TB than white children (Table 16, overleaf). Most cases of childhood TB are not culture confirmed, despite microbiological investigations. It will be important to match the BPSU and the enhanced surveillance datasets to examine the cases that each system captures and misses.

Funding

Centre for Child Health, Royal London Hospital.

Ethics Approval

This study has been approved by the South West MREC.

Support Group

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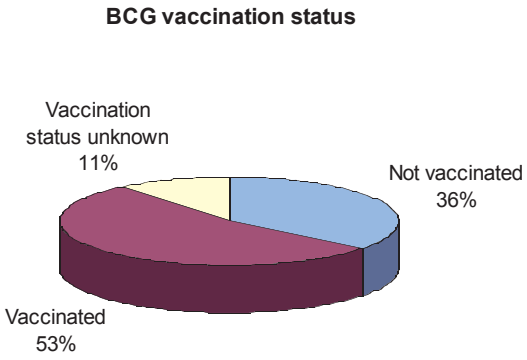

Figure 25: BCG vaccination status

Table 16: Rates of TB notifications < 16 years within the UK*

		Cases	Population	Cases per 100,000
Ethnicity	White	88	10,068,819	0.87
	Indian subcontinent	123	609,912	20.2
	Black African	109	145,956	74.7

*Excluding Ireland as no ethnicity data currently available

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Thyrotoxicosis in Childhood

Key Points

- To determine the incidence of thyrotoxicosis in childhood, clinicians are being asked to report all new cases of thyrotoxicosis seen in children under 16yrs.
- Preliminary results are available for the first 4 months of the study.

Background

The incidence of thyrotoxicosis in children in the UK and the Republic of Ireland is not known. Graves' disease is known to be the commonest cause of thyrotoxicosis in the general population (60-90% of cases worldwide), followed by rarer causes such as solitary thyroid adenomas, multinodular goitre and, in neonates, congenital Graves' disease. Data from other countries in Europe report incidences of Graves' disease in childhood from 0.79/100,000 per year (Denmark)[1] to 8/100,000 per year (Iceland, 10-19 yr olds)[2]. The incidence in Hong Kong was recently reported as 6.5/100,000 per year[3]. The mean age of diagnosis there has been reported as 11.34 years with a female:male ratio of 5.5:14.

In some countries the incidence of Graves' disease is increasing and increased dietary intake of iodine has been implicated[4,5]. Other than this the aetiology of Graves' disease is unknown, but genetic susceptibility, puberty and emotional stress are known contributing factors[6]. The pattern of practice in investigating thyrotoxicosis is not clear. The gold standard for detecting primary hyperthyroidism is a suppressed thyroid stimulating hormone (TSH), but diagnosing the underlying condition may be more difficult. Clinicians may rely on history, clinical findings and basic thyroid function tests to diagnose Graves' disease, or they may wish to investigate further to distinguish it from the other rarer forms of thyrotoxicosis in childhood which may present with identical symptoms and signs. Treatment options for the child with Graves' disease are medical (antithyroid drugs), surgery and radioiodine. Worldwide debate over the safest and most effective use of these treatments in children continues, but historically in Europe antithyroid drugs have been favoured[7].

This study aims to be a comprehensive survey of childhood thyrotoxicosis in the UK and Ireland in order to collect data on the current incidence, patterns of presentation and management of this disease.

Objectives

To identify

- the incidence of childhood Graves' disease in the UK and Ireland.
- the incidences of the other causes of childhood thyrotoxicosis, in the UK and Ireland.
- the presenting features of thyrotoxicosis in children.
- how children with thyrotoxicosis are initially managed in the UK and Ireland.

Surveillance Period

September 2004 - September 2005 (inclusive).

Methodology

Paediatricians are asked on a monthly basis to report all cases meeting the case definition through the orange card system. Paediatricians reporting a case are sent a questionnaire seeking demographic details and clinical features. On completion of the surveillance period, we will determine the incidence and presenting patterns of the various causes of thyrotoxicosis.

Case definition

Any child less than 16 years of age who in the opinion of the notifying paediatrician has thyrotoxicosis, based on history, clinical and laboratory findings.

Denominator Source: Population estimates are based on: UK: Mid-2003 Population Estimates from Office for National Statistics (11,712,200 children <16yrs) Ireland: census 2002 data (888,310 children <16yrs) (Central Statistics Office, Ireland).

Based on an incidence of 0.79/100,000 cases per year (Denmark[1]). *Graves' disease*: 90 cases per year in the UK and seven cases per year in Ireland.

Alternative Data Sources

It is likely that a small number of children with thyrotoxicosis presenting in the older age range covered by the study, i.e. 14-16 yr olds, will be treated as adults and will be referred for diagnosis and treatment to a general endocrinologist. These children will therefore not

be notified via the orange card system by paediatricians. General endocrinologists practising in the UK and Ireland have therefore also been informed of the study through the British Society for Paediatric Endocrinology and Diabetes, Society for Endocrinology, British Thyroid Association, The Irish Endocrine Society and British Endocrine Societies annual conference and will also be sent the questionnaire when they report cases.

Analysis

Preliminary results of the first four months are reported. During the period September 2004 to January 2005 there were 34 confirmed cases of childhood thyrotoxicosis in the UK and one confirmed case in Ireland. Confirmation of a further 18 reports from the UK and four from Ireland is awaited. All reports were notified via the orange card. On the basis of confirmed cases, the estimated annual incidence of thyrotoxicosis would be 1.35 per 100,000 (0-15 yr olds) for the UK and Ireland. The underlying causes are: Graves' 74%; Hashimoto's 11%; Congenital 3%. These clinical diagnoses may be subject to change when follow-up data at one year becomes available. In Graves' disease the mean age at diagnosis is 12.4yrs. There were five prepubertal cases (F:M ratio of 1.5:1) and 18 post-pubarche cases (F:M ratio of 5:1). A variety of presenting symptoms were reported, with the commonest being 'change in behaviour' (40%) or weight loss (37%). The commonest signs were goitre (57%) and tremor (43%). Without exception, paediatricians planned medical treatment for confirmed cases.

Discussion

These preliminary findings show a similar incidence of Graves' disease to other countries in Europe, and confirm a sharp increase in the incidence in girls after the onset of puberty. The practice of managing thyrotoxicosis with drugs alone is confirmed by the preliminary results although this may be subject to change and we await follow up data at one year post diagnosis.

Funding

RCPCH Sir Peter Tizard Research Bursary.

Ethics Approval

This study has been approved by the Scottish MREC.

Support Groups

The British Thyroid Foundation, PO BOX 97, Clifford, Wetherby, LS23 6XD. Tel: 0807 770 7933. Website: http://www.btf-thyroid.org.

Acknowledgements

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6 New Studies 2005

Early onset eating disorder in children under 13 years

Background

Early-onset eating disorders (EOED: defined as onset before 13 years of age) are equally as likely to present to paediatricians as child psychiatrists in the UK.(1) Management of these frequently extremely ill children is complicated by a lack of knowledge of the breadth of the problem, difficulties with recognition of eating disorders in this age group(2) and ongoing debate over the role of paediatricians versus mental health professionals. Nevertheless, clinical experience suggests that children with EOED are very frequently admitted to paediatric wards before referral to child mental health services.

Epidemiological studies suggest that the incidence of eating disorders, including anorexia nervosa (AN), has been increasing in adolescents over the last 50 years.(3) Work has focused on the peak ages of onset (15 years for AN and older for bulimia nervosa). Specialist services have recognised they are seeing increasing numbers of EOED cases, yet no incidence estimates are available for this specific age group. The only recent incidence data for eating disorders in the UK were obtained from a GP register study of all age groups undertaken in the early 1990s. Incidence of AN was estimated as 17.5/100,000 in 10-19 year olds, and 0.3/100,000 in 0-9 year olds. For BN the rates are 20.5/100,000 and 0/100,000 respectively (4). Retrospective studies from the US and Denmark have suggested higher figures, e.g. 9-27 per 100,000 10-14 year girls and 3.7 per 100,000 for boys.(5;6)

The ambiguous position of EOED between paediatrics and mental health has led to significant gaps in knowledge about the extent of this problem. The recent Department of Health National Inpatient Child & Adolescent Psychiatric survey (NICAPS)(7) showed that eating disorders were the commonest diagnosis amongst psychiatric inpatients, and that 9.2% of these (12 patients) were under 13 years. Notably these figures did not include children on paediatric wards, and there is no information on the scale of paediatric resource use by this patient group. A recent national survey of child psychiatrists showed that when a young person with an EOED needed admission, it was most likely to be to a paediatric ward. (Dasha Nicholls, unpublished data).

The recently published National Institute of Clinical Effectiveness (NICE) guidelines on the treatment of eating disorders highlight the lack of quality evidence regarding the epidemiology and treatment of EOED and the importance of greater coordination between professionals involved in their care. This study will, amongst other things, provide insight into how care is provided for EOED across the UK and Ireland

Objectives

1. To estimate the incidence of early onset eating disorders in children in the British Isles
2. To describe the age, sex and family history
3. To describe the range of clinical features at presentation including other psychiatric illness
4. To delineate patterns of professional involvement (paediatric & child mental health)
5. To characterise the range of acute medical complications experienced by children with early onset eating disorders
6. To identify the range of therapeutic interventions used in management.

Surveillance Period

March 2005 - March 2006 (13 months)

Methodology

Consultant paediatricians and child & adolescent psychiatrists will be asked on a monthly basis to report all cases meeting the case definition, through the orange card system. In order that maximum information is obtained and cases not missed, reporting by more than one clinician is encouraged where applicable. Clinicians reporting a case will be sent a questionnaire seeking demographic details and clinical features. For all valid cases a second questionnaire will be sent to the reporting clinician a year after the case was first reported.

Case definition

Please report any child aged 5 -13 years inclusive, newly diagnosed with early onset eating disorder which is defined as:

TWO OR MORE OF THE FOLLOWING

- weight loss or failure to gain weight during a period of expected growth, not due to any identifiable organic cause
- determined food avoidance
- fear of weight gain
- preoccupation with body weight or energy intake
- self induced vomiting
- excessive exercising[1]
- recurrent episodes of binge eating or abuse of laxatives

[1]Exercise may be considered to be excessive when it significantly interferes with important activities, when it occurs at inappropriate times or in inappropriate settings, or when the individual continues to exercise despite injury or other medical complications." (American Psychiatric Association. DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, D.C.: American Psychiatric Association; 2004; pp. 590-591.) This definition has been included in the questionnaire.

Funding

Hyman Wingate Foundation

Ethics approval

The London MREC has approved this study.

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Methicillin-resistant Staphylococcus aureus (MRSA) in children

Background

Routine national surveillance has identified a worrying increase in Methicillin-resistant Staphylococcus aureus (MRSA) bacteraemia, with the number of reported cases rising from 4 in 1990 to 77 in 2000[1]. Over half of the 376 cases of MRSA bacteraemia in children reported between 1990 and 2001 involved infants less than 12 months of age, although substantial numbers of infected infants aged one to four years were also reported.

As the above data were derived from voluntary reporting of cases they almost certainly reflect an under-estimate of the true incidence of infection.

The main aim of this study is to obtain a robust estimate of the incidence of MRSA bacteraemia in children. In addition the study aims to define the demographic and descriptive epidemiological features of the patient population, in particular, the proportion of cases that are either healthcare-associated or community-acquired. Infections due to MRSA have historically been primarily acquired in hospitals, however, in the last few years, there have been reports from other countries, particularly the USA, of MRSA infections in children that have been acquired in the community and which have no demonstrable links to the hospital environment[2-5].

The consolidation of microbiological, epidemiological and clinical information will allow us to determine if community-acquired MRSA bacteraemia has emerged in the UK. These findings will have significant implication for the

management of severe paediatric infections due to S. aureus in the community.

Objectives

The study aims to

- determine the incidence of Methicillin-resistant Staphylococcus aureus (MRSA) bacteraemia in children aged <16 years.
- determine whether the incidence of MRSA bacteraemia varies between children of different ages.
- document the spectrum of clinical features and patterns of presentation of MRSA bacteraemia in children.
- determine whether MRSA bacteraemia in children is mainly nosocomial in origin or is a community-acquired infection.
- determine whether cases of MRSA bacteraemia in children tend to occur in particular hospital units or specialties.
- determine whether strains of MRSA that cause bacteraemia in children have particular biological characteristics. In particular:
    i. Are the strain types similar to those found in hospitalised adults?
    ii. Are the strain types similar to those associated with community-acquired infections reported from other countries?
    iii. Do the strains possess particular virulence traits, such as Panton-Valentine leucocidin?

Surveillance Period

June 2005 - June 2006 (13 months).

Methodology

Paediatricians will be asked on a monthly basis to report all cases meeting the case definition via the Orange card system. Paediatricians will then be sent a questionnaire seeking demographic details and clinical information.

In addition to cases ascertained through the BPSU, cases will also be sought using the following sources:

1. Reports of MRSA bacteraemia routinely reported to the Health Protection Agency (HPA) from hospitals in England, Wales and Northern Ireland.
2. Cases of MRSA bacteraemia in children reported to the HPA, Health Protection Scotland or the National Disease Surveillance Centre (Dublin) by hospitals participating in the European Antimicrobial Resistance Surveillance System (EARSS), a pan-European surveillance programme looking at antimicrobial resistance in a number of pathogenic bacteria including S. aureus. About 30 hospitals in England and Wales, and all hospitals in Scotland and the Republic of Ireland participate in EARSS.
3. Cases identified following referral of blood culture isolates of MRSA from children to reference laboratories including the HPA Laboratory of Healthcare Associated Infection or the HPA Antimicrobial Resistance Monitoring and Reference Laboratory (based on the same site in London), the Scottish MRSA Reference Laboratory (Glasgow) or the National MRSA Reference Laboratory (Dublin).

Case definition

Isolation of methicillin-resistant Staphylococcus aureus (MRSA) from blood cultures of children less than 16 years of age.

Funding

Department of Health.

Ethics approval

The Eastern MREC has approved this study.

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Scleroderma in childhood

Background

Scleroderma is well described in children as well as in adults, and is associated with significant morbidity and mortality[1,2,3]. While some children with scleroderma have systemic sclerosis (SSc), more commonly scleroderma in children is localised (often referred to as morphoea) in that it is confined to the skin and underlying tissues. Other rare variants of scleroderma including eosinophilic fasciitis can also occur. Although localised scleroderma (as opposed to SSc) is not a multisystem connective tissue disease, it can be severely debilitating. Subcutaneous tissues, muscle and bone as well as skin can be affected. Further, if the affected area crosses a joint, for example knee or elbow, then contracture and growth retardation can occur. In addition, the lesions can be very disfiguring, especially if the face is involved.

There are no data on the occurrence of childhood scleroderma which would inform the level and distribution of expert provision required to manage affected children. Our primary aim is to ascertain the incidence of childhood scleroderma in its different forms. In addition, we aim to address a number of other questions in relation to the occurrence of these disorders, including the delay between symptom onset and diagnosis, evaluation of the pattern of care received by the affected children prior to diagnosis and consideration of how this might be enhanced

Objectives

The study aims to identify

- the incidence of childhood scleroderma, in its different forms, in the United Kingdom.
- the delay between symptom onset and diagnosis.
- the pattern of care received by the affected children before and after diagnosis? How might this be enhanced.
- the spectrum of disease in the UK and Ireland. Specifically:
  a. the ages which are most affected
  b. the male: female ratio of affected children, and does this vary with age
  c. any major regional variations.

Surveillance Period

July 2005 - July 2006 (13 months).

Methodology

Paediatricians will be asked on a monthly basis to report all cases meeting the case definition via the Orange card system. Paediatricians will then be sent a questionnaire seeking demographic details and clinical information.

While it is anticipated that the BPSU will be the main source of case ascertainment, it is recognise that some children with scleroderma may be referred directly to adult rheumatologists

or dermatologists with an interest in scleroderma. Thus ascertainment questionnaires/proformas will also be sent to members of the British Society for Paediatric and Adolescent Rheumatology, the British Association of Dermatologists, and the UK Scleroderma Study Group.

Two rather than one questionnaire(s) are being sent to reporting clinicians, at both first mailing and 12 months. This is because we are including a slightly modified version of the Paediatric Rheumatology European Society (PRES)[5], questionnaire. In addition paediatricians are being asked to state whether the diagnosis has been confirmed by a dermatologist or paediatric rheumatologist (and this may change between first mailing and 12 months).

Follow-up questionnaires will be sent at 12 months. The reporting clinician will be sent a photocopy of their original response, asking them to mark on any change in the 12 month period and/or update previous entries.

Case definition

All cases of abnormal skin thickening (the skin will usually be difficult to pinch normally) suspected by the reporting paediatrician to be scleroderma (age up to 16 years).

For confirmation of cases, we propose to ask in the follow-up questionnaire if a dermatologist or paediatric rheumatologist has confirmed the diagnosis.

Funding

Raynaud's and Scleroderma Association.

Ethics Approval

The South Manchester REC has approved this study.

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7 International Network of Paediatric Surveillance Units (INoPSU)

Figure 26: International Network of Paediatric Surveillance Units (INoPSU)

Background

Following the success of the BPSU, the same methodology was adopted and adapted in the 1990s to other countries whose paediatric services are amenable to an active surveillance approach. Within Europe this led in 1992 to units in the Netherlands and Germany and 1994 in Switzerland. The European paediatric surveillance units then met and communicated regularly in order to discuss surveillance protocols.

The European initiative was also the stimulus for the development in 1992 of an Australian unit and later the Malaysian unit (1994) to be followed more recently by Units in Canada (1996), Papua New Guinea (1996), New Zealand and Latvia (1997) and Portugal (2001) and Greece/Cyprus (2003). Wales (1995) and Ireland (1997) developed surveillance units using a similar methodology to the BPSU, though they are concentrating on less rare disorders.

Through the use of active ascertainment the fourteen units provide an efficient, effective framework for case-finding for investigators who wish to study rare conditions in children. These include infections, infection-related conditions, vaccine-preventable diseases, congenital and inherited (genetic) diseases, unusual injuries or therapies and rare complications of common diseases. The units frequently encourage, facilitate or elicit studies but only occasionally undertake research themselves.

In 1996 the proposal to form an International Network of Paediatric Surveillance Units (INoPSU) was accepted in principle by all units existing at that time. Now all the units contact each other for results, sharing of protocols, putting researchers in touch with each other and a common international report is shared as part of national reports.

The Network was formed at a meeting in August 1998 when the 10 units expressed a desire to link with each other. This took place at the 22nd International Congress of Paediatrics in Amsterdam, The Netherlands. The first INoPSU conference was held in June 2000 in Ottawa, Canada. At the second INoPSU meeting in York, UK, the British Ophthalmology Surveillance Unit was accepted as an affiliate member of the network.

The mission of INoPSU is the advancement of knowledge of uncommon childhood infections and disorders and the participation of paediatricians in surveillance on a national and international basis so as to achieve a series of benefits. A document to be known as the Amsterdam-Ottawa Note detailing the functions and structure of the network has been agreed and has been posted on the INoPSU website at http://www.inopsu.com.

April 2004 saw the 3rd INoPSU conference, held in Lisbon, Portugal. At the meeting it was agreed that the current convenor, Professor Elizabeth Elliott (APSU), would step down to be replaced by two co-convenors, Professor Rudi von Kries (Germany) and Dr Robert Pereira (Netherlands). Richard Lynn (UK) would act as communications liaison between the units. The meeting also received a report of the newly developing units, most notably Trinidad and Tobago, with interest also being shown in Argentina and Poland. A full report of the 3rd INoPSU conference is available from the 18th BPSU annual report. The 4th INoPSU conference will be held in London in May 2006.

Details on the activities of each surveillance unit is available form their respective website and also from the INoPSU website (www.inopsu.com). The INoPSU site has just been updated and includes details on each of the individual units, INoPSU reports and details on all studies undertaken (Figure 27, overleaf).

Figure 27: INoPSU Website homepage

Table 17: National paediatric surveillance units

Country	Child population (10^6- aged 0-15 years)	Established	Respondents	Reply paid **(E-mail reporting)	Response rate	Study fee
Australia	3.9	1992	1042	Yes	96%[1]	Yes
UK/Rep of Ireland	12.8	1986	2324	No	92%	Yes
Canada	7.5	1996	2335	Yes	83%	Yes
Germany	12.0	1992	468*	No	98%	Yes
Latvia	0.4	1996	22	No	70%	No
Malaysia	7.7	1994	395	Yes	75%[2]	No
Netherlands	3.0	1992	640	Yes	95%[3]	Yes
Papua New Guinea	2.0	1996	40	Yes	79%	No
New Zealand	0.8	1997	165	Yes	95%[4]	No
Switzerland	1.3	1995	40*	Yes	100%	No
Wales	0.65	1994	1295	No	94%[5]	No
Republic of Ireland	1.0	1996	135	Yes	85%	Yes
Portugal	1.8	2001	1500	Yes	30%	Yes
Greece/Cyprus	1.6	2001	310	No	93%	No

1 538 (52%) from a total 1042 clinicians reported to the APSU by email in 2001.

2 MPSU is temporarily closed.

3 Respondents reply either by reply-paid card (30%) or to an email (70%) depending on their preference. Telephone notification of AFP is also requested.

4 Since January 2002, approximately 30% of paediatricians have received their card via email.

5 Also temporary members: Consultant Rheumatologists 21, Ophthalmologists 28.

Appendix A – Completed Studies 1986-2004

By mid-2004 the BPSU had completed 58 studies. Information about these studies has been included in previous annual reports of the BPSU, which are available from the BPSU office and are also listed on the BPSU website. Information on studies completed from 2000, principal investigators and definitive papers are listed overleaf.

X-linked anhydrotic ectodermal dysplasia

Haemorrhagic shock encephalopathy syndrome

Haemolytic uraemic syndrome I

Kawasaki disease

Lowe syndrome

Neonatal herpes I

Insulin dependent diabetes in under fifteens

Drowning and near drowning

Galactosaemia

Congenital toxoplasmosis

Higher order births

Acute rheumatic fever

Rett syndrome

Measles, mumps, rubella-meningococcal meningitis

Chemistry set poisoning

Acute flaccid paralysis

Androgen insensitivity syndrome

Long term parenteral nutrition

Insulin dependent diabetes in under fives

Juvenile dermatomyositis

Congenital dislocation of the hip

Haemophagocytic lymphohistiocytosis

Non-accidental poisoning/ Munchausen syndrome by proxy

Neonatal necrotising enterocolitis

Vitamin K deficiency bleeding I - II

Biliary Atresia

Transient and permanent neonatal diabetes

Adverse neonatal outcomes of delivery or labour in water

Congenital syphilis

Congenital cataract

Medium chain acyl-CoA dehydrogenase

Pyroxidine dependent seizures

Neonatal meningitis

Cerebral oedema and death following diabetic ketoacidosis

Hepatitis C virus (HCV) infection

Congenital brachial palsy

Subdural haematoma and effusion

Inflammatory bowel disease in under 20 year olds

Fatal/Severe allergic reactions to food ingestion
Surveillance Period: March 1998 - February 2000
Investigators: Dr A Colver, Dr A Cant, Dr C MacDougal
Published Paper: How dangerous is food allergy in childhood? The incidence of severe and fatal allergic reactions across the UK and Ireland. Macdougall CF, Cant AJ, Colver AF. Arch Dis Child 2002; 86: 236-239.

Invasive Haemophilus influenzae infection
Surveillance Period: October 1992-October 2000
Investigators: Dr P Heath, Dr J McVernon, Professor R Booy
Published Paper: Vaccine failures after primary immunisation with Haemophilus influenza type-b comjugate vaccine without booster. Booy R, Heath PT, Slack MPE, Begg, N, Moxon ER, Lancet,1997; 349:1197-202.

Severe Visual Impairment /Blindness
Surveillance Period: Sept 1999- December 2000
Investigator: Dr JS Rahi, N Cable, on behalf of the British Childhood Visual Impairment Study Group (BCVISG)
Published Paper: Severe visual impairment and blindness in children in the UK. Rahi JS, Cable N. on behalf of the British Childhood Visual Impairment Study Group (BCVISG). Lancet 2003; 362: 1359-65.

Haemolytic Uraemic Syndrome II
Surveillance Period: February 1997- February 2001
Investigators: Dr M Taylor, Dr D Milford, Dr B Adak, Mr R Lynn, Dr M Locking, Dr S O'Brien
Published Paper: Childhood hemolytic uremic syndrome, United Kingdom and Ireland. Lynn RM, O'Brien SJ, Taylor CM, Adak GK, Chart H, Cheasty T, Coia JE, Gillespie IA, Locking ME, Reilly WJ, Smith HR, Waters A, Willshaw GA. Emerg Infect Dis. 2005 Apr;11(4):590-6.

Group B Streptococcal Disease
Surveillance Period: March 2000 - March 2001
Investigator: Dr P Heath
Published Paper: Group B streptococcal disease in UK and Irish infants younger than 90 days. Heath PT , Balfou G Weisner AW, Efstratiou A, Lamagni, TL, Tighe H, O'Connell LAF, Cafferkey M, Verlander NQ, Nicoll A, McCartney CA, on behalf of the PHLS GBS Working Group. Lancet 2004; 363: 292-94.

Reye's Syndrome
Surveillance Period: June 1986 - June 2001
Investigators: Dr S Hall, Mr R Lynn
Published Paper: 15th BPSU Annual Report 2000/01.BPSU London 2001.

Subacute Sclerosing Panencephalitis
Surveillance Period: June 1986 - June 2001
Investigator: Dr E Miler
Published Paper: The epidemiology of subacute sclerosing panencephalitis in England and Wales 1990-2002. Miller C, Andrews N, Rush M, Munro H, Jin L, Miller E. Arch Dis Child. 2004; 89(12):1145-8.

Encephalitis in Early Childhood (2mths–3yrs)
Surveillance Period: October 1998 - September 2001
Investigators: Dr K Ward, Professor E Ross
Published Paper: Human herpesviruses-6 and -7 each cause significant neurological morbidity in Britain and Ireland. Ward, KN, Andrews, NJ, Verity, CM, Miller, E, and Ross, EM. Arch Dis Child 2005; 90: 619-623.

Cerebrovascular disease, stroke and like illness
Surveillance Period: January 2001 - January 2002
Investigators: Dr F Kirkham, Dr A Williams
Published Paper: 17th BPSU Annual Report 2002/03. BPSU London 2003.

Vitamin K deficiency bleeding III
Surveillance Period: January 2002 - January 2003
Investigators: Dr A W McNinch, Dr J H Tripp
Published Paper: 17th BPSU Annual Report 2002/03. BPSU London 2003.

Congenital cytomegalovirus (cCMV)
Surveillance Period: February 2001 - February 2003
Investigators: Dr P Tookey, Professor M-Lnewell, Dr M Sharland
Published Paper: 17th BPSU Annual Report 2002/03. BPSU London 2003.

Thrombosis in childhood
Surveillance Period: February 2001 - February 2003
Investigators: Dr B Gibson, Dr P Bolton-Maggs
Published Paper: 17th BPSU Annual Report 2002/03. BPSU London 2003.

Internal abdominal injury due to child abuse
Surveillance Period: March 2002 - March 2003
Investigators: Dr P M Barnes, Dr C A Norman, Dr A M Kemp, Professor J Sibert
Published Paper: Barnes PM, Norton C M, Dunstan F D, Kemp A M, Yates D. Sibert JR Abdominal Injury due to Child Abuse Lancet 2005; 366: 234-5.

Suspected fatal adverse drug reaction in children
Surveillance Period: June 2002 - June 2003
Investigators: Professor T Stephenson, Dr K Cheng
Published Paper: 17th BPSU Annual Report 2002/03. BPSU London 2003.

Severe complications of varicella (chickenpox) in hospitalised children
Surveillance Period: November 2002- November 2003
Investigator: Dr C Bramley
Published Paper: 18th BPSU Annual Report 2003/04. BPSU London 2004.

Invasive fungal infections in VLBW infants
Surveillance Period: February 2003 - February 2004
Investigator: Dr W McGuire, Dr L Clerihew, Dr T Lamagani
Published Paper: 18th BPSU Annual Report 2003/04. BPSU London 2004.

Appendix B Published papers 2004-2005

Variations in neurodegenerative disease across the UK; findings from the national study of Progressive Intellectual and Neurological Deterioration (PIND). Devereux G, Stellitano L., Verity CM, Nicoll A, Rogers P. Arch Dis Child 2004; 89:8-12.

Is variant Creutzfeldt-Jakob disease in young children misdiagnosed as Alpers' syndrome? An analysis of a national surveillance study. te Water Naude J, Verity CM, Will RG, Devereux G, Stellitano L. JNNP 2004 Vol75 No 5.

Group B streptococcal disease in UK and Irish infants < 90days of age. Heath PT, Balfour G, Weisner AM, Efstratiou A, Lamagni TL, Tighe H, O'Connell LAF, Cafferkey M, Verlander NQ, Nicoll A, AC McCartney. Lancet 2004;363:292-4.

Characterisation of Group B Streptococci from Infants with Invasive Disease in England and Wales. Weisner AM, Johnson AP, Lamagni TL, Arnold E, Warner M, Heath PT, Efstratiou A. Clinical Infectious Disease 2004; 38:1203-8.

HPA. COVER programme: October to December 2003. Vaccination coverage statistics for children up to five years of age in the United Kingdom. Commun Dis Rep CDR Wkly [serial online] 2004 [cited 4 May 2004]; 14 (13)): immunisation.

Available from http://www.hpa.org.uk/cdr/PDFfiles/2004/cdr1304.pdf

Recent trends in HIV and other STIs in the United Kingdom: data to the end of 2002. Brown AE, Sadler KE, Tomkins SE, McGarrigle CA, Scott LaMontagne D, Goldberg D, Tookey PA, Smyth B, Thomas D, Murphy G, Parry JV, Evans BG, Gill ON, Ncube F, Fenton KA. Sex Transm Infect. 2004; 80(3):159-66. Review.

Follow up of children exposed to antiretroviral therapy in pregnancy (CHART): a role for HIV Physicians? BHIVA, Cardiff 2004. Hankin CD, Tookey PA, Lyall EGH, Peckham CS. HIV Medicine 2004, 5 (Suppl.2): P56

HIV-infected adolescents: an evolving UK cohort. BHIVA, Cardiff 2004. Foster CJ, Lyall EGH, Doerholt K, Duong T, Tookey PA, Sharland M, Tudor-Williams G, Novelli V, Butler K, Riordan A, Gibb DM. HIV Medicine 2004; 5 (Suppl.2): O17.

The epidemiology of subacute sclerosing panencephalitis in England and Wales 1990-2002. Miller C, Andrews N, Rush M, Munro H, Jin L, Miller E. Arch Dis Child. 2004; 89(12):1145-8.

Response to highly active antiretroviral therapy varies with age: the UK and Ireland Collaborative HIV Paediatric Study. Walker AS, Doerholt K, Sharland M, Gibb DM, for the Collaborative HIV Paediatric Study (CHIPS) Steering Committee. AIDS 2004; 18:1-10.

Seamless management of biliary atresia in England and Wales (1999-2002). M. Davenport, J. De Ville de Goyet, M. Stringer, G. Mieli-Vergani, D. Kelly, P. McClean, L. Spitz . Lancet 2004; 363: 1354-1357.

Childhood hemolytic uremic syndrome, United Kingdom and Ireland. Lynn RM, O'Brien SJ, Taylor CM, Adak GK, Chart H, Cheasty T, Coia JE, Gillespie IA, Locking ME, Reilly WJ, Smith HR, Waters A, Willshaw GA. Emerg Infect Dis. 2005;11(4):590-6.

Human herpesviruses-6 and -7 each cause significant neurological morbidity in Britain and Ireland. K N Ward, N J Andrews, C M Verity, E Miller, and E M Ross. Arch Dis Child 2005;90: 619-623.

Subdural haematoma and effusion in infancy: An epidemiological study. C J Hobbs, A Childs, J Wynne, J Livingston, A Seal Arch Dis Child 2005 (in press).

Human herpes viruses-6 and -7 each cause significant neurological morbidity in Britain and Ireland. Ward KN, Andrews NJ, Verity CM, Miller E, Ross EM. Arch Dis Child. 2005;90;619-62233.

Unexpected Occasional Persistence of High levels of HHV-6 DNA in Sear: Detection of Variants A and B. Ward KN, Thiruchelvam AD, Couto-Parada X. Journ Med Virol 2005. 76:563-570.

Severe food-allergic reactions in children across the UK and Ireland, 1998-2000. Colver AF, Nevantaus H, Macdougall CF Cant AJ. Acta Paediatrica 2005; 94: 689-695.

Appendix C Presentations 2004-2005

RCPCH Annual Scientific Meetings 2004 and 2005

Invasive fungal infections in very low birthweight infants: United Kingdom national surveillance study. Clerihew, Lamagni T, Brocklehurst P, Balfour A, McGuire W. York 2004. Arch Dis Child 2004; 89 (Suppl 1). A1-A7.

Hankin CD, Tookey PA, Lyall EGH, Peckham CS. Follow up of children exposed to antiretroviral therapy in pregnancy (CHART). York 2004. Arch Dis Child 2004; 89 (Suppl 1): A76.

Severe complications of chickenpox in hospitalised children. Cameron JC, Allen G, Johnston F, Booy R, Heath PT, Finn A. York 2005. Arch Dis Child 2005;90 (Suppl II):A1-A8.

Abdominal injury due to child abuse: Final results from the BPSU study. Sibert JR, Barnes PM, Norton C, Yates D, Dunstan FD, Kemp AM. York 2005. Arch Dis Child 2005;90 (Suppl II):A1-A8.

The UK prospective study of cerebral oedema complicating diabetic ketoacidosis. Edge JA, Jakes R, Roy Y, Widmer B, Ford-Adams ME, Murphy NP, Bergomi A, Dunger DB. York 2005. Arch Dis Child 2005;90 (Suppl II):A1-A8.

The essential role of all UK Paediatricians in performing surveillance for vCJD via the study of progressive intellectual and neurological deterioration (PIND). Verity CM, Stellitano L, Winstone AM, Nicoll A, Will RG. York 2005. Arch Dis Child 2005;90 (Suppl II):A1-A8.

Severe hyperbilirubinaemia in the newborn: The first year of surveillance. Manning DJ, Todd PJ, Maxwell MJ. York 2005. Arch Dis Child 2005;90 (Suppl II):A1-A8.

International Network of Paediatric Surveillance Units 3rd Conference Lisbon 2004.

Invasive fungal infections in very low birthweight infants: United Kingdom national surveillance study. Clerihew, Lamagni T, Brocklehurst P, Balfour A, McGuire W. Lisbon, April 2004. Portuguese Paediatric Surveillance Bulletin Vol 5 No 1 June 2004.

Surveillance of Haemolytic Uraemic Syndrome HUS): An international collaboration. Elliott E, Lynn RM, Schmidt H, Proulx F, Wong W, Socket P, Siva JE, Adak R, on behalf of members of the Australian, British, Canadian, New Zealand, Swiss and Portuguese Paediatric Surveillance Unit's/ HUS study groups. Lisbon, April 2004. Portuguese Paediatric Surveillance Bulletin Vol 5 No 1 June 2004.

The International Network of Paediatric Surveillance Units (INoPSU). Elliott E, Lynn RM on behalf of INoPSU Secretariat, Member and Associate Units. Lisbon, April 2004. Portuguese Paediatric Surveillance Bulletin Vol 5 No 1 June 2004.

Beyond Counting numbers - Demonstrating public health impacts of paediatric surveillance. Grenier D, Preece M, v Kries R, Pereira R, on behalf of the participants and investigators of the Canadian, British, German and Netherlands Paediatric Surveillance Units. Lisbon, April 2004. Portuguese Paediatric Surveillance Bulletin Vol 5 No 1 June 2004.

Public Health Outputs of the British Paediatric Surveillance Unit. Lynn RM, Preece M. Lisbon, April 2004. Portuguese Paediatric Surveillance Bulletin Vol 5 No 1 June 2004.

How to represent reporting physicians on the final papers - Authourship and citations. Lynn RM, Preece M. Lisbon, April 2004. Portuguese Paediatric Surveillance Bulletin Vol 5 No 1 June 2004.

Completeness of Ascertainment of Case Reports in Active Surveillance. Knowles R, Smith A, Lynn RM. Lisbon April 2004.

Other Conferences & Meetings

"Is variant CJD hidden among children with undiagnosed progressive intellectual and neurological deterioration (PIND)? Findings from a national surveillance study" British Paediatric Neurology Association Annual Meeting, Verity C. Sheffield 23-25 January 2004.

Childhood Stroke in the United Kingdom and Eire - a descriptive epidemiological study (Poster). Williams A, Kirkham F. British Paediatric Neurology Association Annual Meeting. Sheffield 23-25 January 2004.

Childhood Stroke in the United Kingdom and Eire - a descriptive epidemiological study (Poster). Williams A, Kirkham F. American Medical Association Meeting San Diego February 2004.

National collaborative study of newborn screening for MCADD. Dezateux C, Oerton J. Pamela Phillips Annual meeting of BIMDG, Glasgow July 2004.

Langerhan CellHistiocytosiis Surveillance Report. Histiocyte Society 20th Annual Meeting Stockhom September 2004. Pediatric Blood & Cancer. 2005; Vol 45, Issue 1: Abstracts (p 88-100).

UK Collaborative Study of Newborn Screening for MCADD. Dezateux C, Oerton J. Pamela Phillips UKNSLN Annual Meeting, Birmingham Feb 2005.

Experience in screening for MCADD. Dezateux C, Oerton J. Pamela Phillips. Poster presentation, Euromedlab, May 2005.

Appendix D Membership of Executive Committee 2004/2005

Professor Mike Preece	Chair
Dr Claire Cameron	Health Protection Scotland
Dr Allan Colver	Co-opted
Dr Hugh Davies	Co-opted
Professor Carol Dezateux	Institute of Child Health (London)
Professor Denis Gill	Royal College of Physicians (Ireland)
Dr Alun Elias-Jones	Royal College of Paediatrics and Child Health Treasurer
Ms Linda Haines	Royal College of Paediatrics and Child Health Research Division
Dr Rachel Knowles	Medical Adviser (non-communicable disease)
Dr Gabrielle Laing*	Co-opted
Mr Richard Lynn	Scientific Co-ordinator
Dr William McGuire*	Co-opted
Professor Neil McIntosh	Royal College of Paediatrics and Child Health Research Division
Dr Richard Pebody	Health Protection Agency
Dr Martin Richardson	Co-opted
Dr Alan Smith	Medical Adviser (communicable disease)
Professor Stuart Tanner	Department of Health (observer)
Mrs Carol Youngs*	Patient and Carers Committee representative

* Stepped down in 2005