Royal College of Paediatrics and Child Health
British Paediatric Surveillance Unit

18th Annual Report, 2003-2004

BPSU

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British Paediatric Surveillance Unit – Annual Report 2003-2004

Compiled and edited by Richard Lynn, Rachel Knowles, Mike Preece, and Alan Smith, September 2004

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Stepped down in 2003

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by Professor Mike Preece,

Chairman of the BPSU Executive Committee

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Foreword

This past year has been one of great activity for the BPSU and some aspects of this continue into next year. Apart from our regular processes we are in discussions about our methodology and funding.

The issues about methodology stem from recent changes in the laws that govern confidentiality and privacy. A key feature of the way that data for BPSU projects are gathered is that they are obtained without consent. This is important for two principle reasons. Firstly, all our studies concern rare paediatric disorders and a small number of returns missed because of withheld consent could not only skew estimates of incidence, but reduce the accuracy and undermine the veracity of results from any study. Secondly, as the data are collected retrospectively, month by month, the need for consent would involve much more work for our responding paediatricians. So much so that we have always felt that there would be a significant dip in ascertainment if consent were needed. This is clearly accepted by the MRECs that review our projects.

Recent changes in law, particularly the Data Protection Act 1998 and the Health and Social Care Act 2001 have now made us more concerned about our position concerning consent. Many other surveillance systems (for example the Cancer Registers) have similar concerns. For this reason we are pursuing a provision in the Act (Section 60) that in special cases allows particular surveillance systems to collect non anonymous data without consent; this is closely monitored by a statutory body, the Patient Information Advisory Group. We have started the process of applying for exemption so that the BPSU can continue to operate using its current methodology. In the meantime our current position and recommendations concerning ethics and confidentiality can be found on our website (http://bpsu.inopsu.com/ethics.html). A key element of this is the use of minimal identifiers to allow discounting of duplicate returns and the rendering of the data set anonymous as soon as possible.

For the past three years we have had partial funding from the Department of Health for the running of the Unit. This funding comes to an end this year and we have started negotiations with the Department for continuation of financial support. We have already had a helpful meeting with representatives of the Department and this continues over the next few months.

An exciting new initiative starts this year: the first winner of the Sir Peter Tizard Research Bursary commences his project. This is Dr Scott Williamson of Ninewells Hospital, Dundee who will be studying the incidence and other features of childhood thyrotoxicosis using the BPSU system. The Bursary of £15,000 covers the BPSU fees and the costs of some local research assistance in Dundee. The Bursary is named after one of the founders of the BPSU and supported by the College, for which we are very grateful. We have already had an encouraging number of applications for this year's award. Other new studies projected to start this year are neonatal herpes simplex infection, medium chain acyl CoA dehydrogenase deficiency, non-type 1 diabetes mellitus and early onset eating disorders.

Two longstanding studies continue: HIV/AIDS and progressive intellectual and neurological deterioration. These are particularly time consuming for reporting paediatricians and we wish to register our thanks for their continued support.

On the international front, the 3rd meeting of the International Network of Paediatric Surveillance Units (INoPSU) was held in Lisbon in April 2004. This was much appreciated by all who attended and is now established as a bi-annual meeting. The BPSU continues to contribute to the INoPSU Executive, with Richard Lynn, our scientific coordinator taking on the role of communications liaison.

Work is now complete on the creation of two BPSU information leaflets. One is for the paediatric community and the second for members of the public. The latter is part of our drive to raise public awareness and understanding of the work of the BPSU. These will be distributed in the very near future.

There have been a number of changes to the Executive Committee. Dr Hilary Kirkbride has stepped down after three years as infectious diseases medical adviser to be replaced by Dr Alan Smith of the Health Protection Agency. Professor Stuart Tanner has replaced Dr Simon Lenton, paediatric adviser to the Department of Health. Lastly after 10 years, Professor Angus Nicoll steps down as the Health Protection Agency representative to be replaced by Dr Richard Pebody. In the office we say goodbye to Myra Schehtman who leaves after 17 years as the administrative assistant, and thank her for her hard work over the years.

Finally, I would like to thank all those that make the BPSU work: the members of the Executive Committee; the administrative staff of the College; the investigators who initiate and execute the studies; but most of all the more than 2,400 paediatricians who complete the cards every month.

Professor Mike Preece

Chairman of the BPSU Executive Committee

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, the Communicable Disease Surveillance Centre (CDSC), the Centre for Epidemiology and Biostatistics at the Institute of Child Health, London, the Scottish Centre for Infection and Environmental Health (SCIEH), 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 in the boxes below.

This report mainly focuses on activities undertaken during the year 2003. Reference is also made to studies and activities, which have already commenced in the year 2004.

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
- respond rapidly to public health emergencies.

June 1995 - adapted from prior documentation

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 common disease) or 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 of which can now be downloaded from the website at http://bpsu.inopsu.com/methodol.htm or is 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 research objectives. Once approved by the BPSU Executive, 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 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 definition 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.

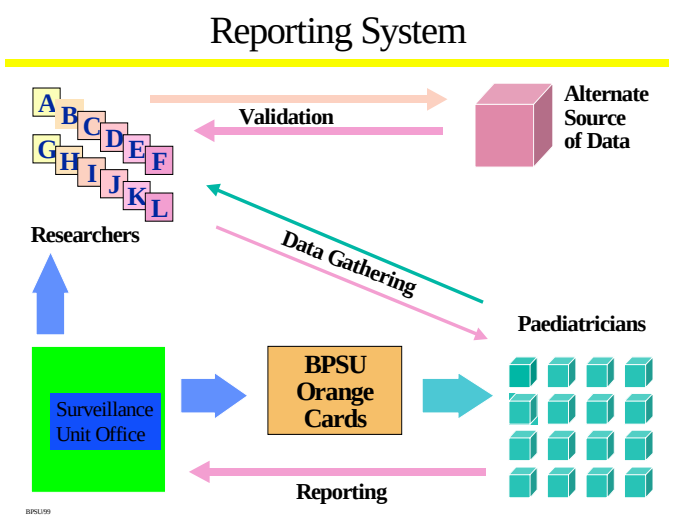
Respondents are asked to return the card to the BPSU office, indicating the number of cases of each condition on the card, which they have seen during the preceding calendar month. Scottish paediatricians return their completed cards via the Scottish Centre for Infection and Environmental Health. When reporting a positive case, respondents are also asked to complete the clinicians' tear-off section making a note of the case and **keeping** the details for future reference. This is required, as 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, the BPSU office is never in possession of 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 and identifying duplicate case reports - see Figure 1. 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 duplication than miss the chance of receiving a report.

Figure 1



The speed with which investigators receive survey data, identifying incorrect reports or duplicates and confirm the cases is known as the **'completion rate'**. Table 2 (page 8) shows the number of cases reported to the BPSU from its inception until the end of year 2003 for all the conditions under surveillance at June 2003. 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 for all studies in 2003 was high. For example, of the conditions under surveillance at June 2003, only 191 (3%) of the 5,943 case reports had yet to be followed-up. The final completion rate normally averages between 90-98%.

Table 3 (page 8) summarises the outcome of the follow-up of all cases reported to the BPSU by the end of year 2003 and provides evidence for the level of accuracy of reporting by participating clinicians.

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,

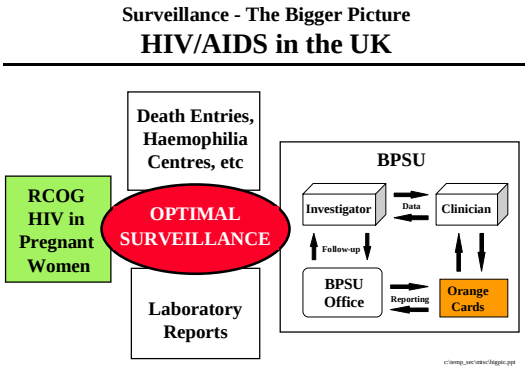
and

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 2004).

Figure 2



Where necessary to improve case ascertainment, consultants working in a number of other specialties have been invited to participate in the scheme or in a parallel surveillance system. For example since 1992, pathologists have been included in the BPSU reporting scheme, whilst most studies of infections also use laboratory reports from microbiologists e.g. HIV/AIDS and congenital rubella. As well as improving case ascertainment, such complementary data sources help to validate the surveillance system (Figure 2).

Funding

For the three-year period to September 2004 the BPSU was is in receipt of a grant from the Department of Health (DH). This contribution supported a substantial percentage of the Unit's running costs. An extension to this grant is currently being sought. In addition, the BPSU asks stufy teams to contribute a sum to cover the printing/distribution of the orange cards, and where possible the administrative costs of coordinating the study. This sum is currently £7,600 for a 13-month study, though a lower rate of £3,900 exists for those who are applying for funds from small local sources.

Further non-cost support is received from the Royal College of Paediatrics and Child Health, the Health Protection Agency (Communicable Disease Surveillance Centre), the Institute of Child Health (London), and the Scottish Centre for Infection and Environmental Health.

3 Surveillance activities in 2003

Four studies commenced in 2003. February saw the start of a thirteen-month study into invasive fungal infection in very low birthweight infants. In June, surveys into severe hyperbilirubinaemia in the newborn and Langerhans cell hystiocytosis were commenced. Finally, a fourth study, tuberculosis in childhood, started in December.

Four studies in 2003 had their period of surveillance extended for a further year, HIV/AIDS, congenital rubella, progressive intellectual and neurological deterioration (PIND), and congenital toxoplasmosis. Surveillance on six studies ended in 2003, vitamin K deficiency bleeding (January), congenital cytomegalovirus (February), thrombosis in childhood (February), internal abdominal injury due to child abuse (March), suspected fatal adverse drug reaction (June), and severe complications of varicella (November). By June 2003, 55 studies had been completed since the BPSU's inception in June 1986 - listed in Appendix A. Known publications and presentations in 2003/ 2004 relating to these studies and the Unit's work totaled 50 and are listed in Appendices B and C.

Two studies have so far commenced in 2004, neonatal herpes simplex virus infection (January) and medium chain acyl CoA dehydrogenase deficiency (June). Three further studies, thyrotoxicosis, non-type 1 diabetes and early onset eating disorders have been given provisional approval and are expected to commence once MREC approval and funding have been finalised. The study on thyrotoxicosis was the successful submission by Dr Scott Williamson of Ninewells Hospital, for the new competitive bursary, awarded by the RCPCH, in the name of Sir Peter Tizard, the first chair of the BPSU.

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.

Through its position as "server" the BPSU continued to contribute to the work of the International Network of Paediatric Surveillance Units (INoPSU). The first INoPSU progress report was published this year and is available from the BPSU office or via the BPSU website.

Participation in the scheme during the year 2003

The BPSU ascertains the names of new consultants primarily through RCPCH advisory appointment committees, the RCPCH membership office, BMJ adverts, through personal communication and the ongoing College workforce census. During the year, 207 consultants were placed on the mailing list whilst 116 were removed, following retirement. The number of consultant paediatricians participating in the scheme during the year 2003 therefore rose to 2380, an increase of 3.5% on the previous year. It should, however, be noted that some paediatricians who hold consultant status are excluded, as they do not undertake relevant clinical work, or else colleagues report on their behalf. The BPSU mailing list also includes selected groups of consultants other than paediatricians i.e. 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.

Return rates for the orange cards remain high - the overall card return compliance rate for the year 2003, calculated as a proportion of orange cards returned, was 92.3% (27,950/25,803), the same as in 2002. Monthly response rates ranged from 94.1% in April to 89.5% in December, with a median of 92.7%. To maintain this compliance rate, respondents who have not returned cards for two consecutive months are sent letters, to verify postal address and to act as a reminder. Of those responders not returning cards less than 1% are considered as persistent non-responders. The return rate however is considerably higher than any equivalent UK scheme and ranks 7 of the 14 other national paediatric units (Table 18, page 41).

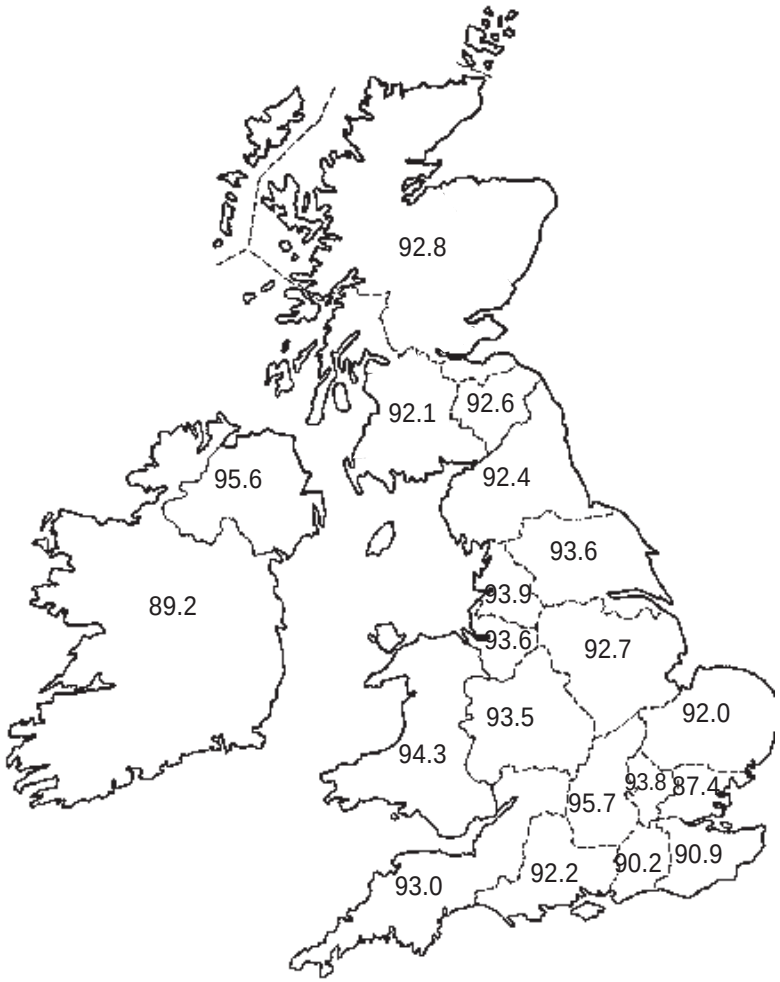
Though variability in compliance exists (Figure 3) the response rate range across the regions has fallen from 12.6% in 2002 to 8.1% in 2003. For the first time Northern Ireland achieved the highest average yearly response rate – 95.6% with Wales ranked second on 94.3%. The Thames area showed a cumulative response rate of 90.6% considerably up on the 87.5% of 2002. With so many teaching hospitals in London there is concern that cases may be going unreported. Although many paediatric specialists receiving the orange card are unlikely to see these conditions and thus may be less likely to return the cards on a regular basis, we would encourage return of the cards to state "no cases" as this markedly improves completeness and ascertainment. With regard to rank order over the year, North

West Thames rose 15 places to rank 4th and the West Midlands rose 7 places to 8th. Notable falls in the ranking were seen, the Republic of Ireland fell 16 places to 19th, East Anglia fell 11 places to 16th and North Scotland fell 10 places from first in 2002 to 10th (Table 1). Overall, the response to the system can still be considered as excellent.

Table 1 *Regional ranking 2002 and 2003*

Region	Rank 2003	Rank 2002
Northern	13	15
Yorkshire	6	7
Trent	11	14
E Anglia	16	5
NWT	4	19
NET	20	20
SET	17	17
SWT	18	18
Wessex	14	11
Oxford	5	3
SWest	9	10
WMids	8	15
Mersey	7	8
NWest	3	6
Welsh	2	2
NScot	10	1
SScot	12	13
WScot	15	11
NIre	1	9
RIre	19	3

Figure 3 *Average orange card return rate (%) by area, 2003*



Workload of those reporting

The BPSU continually monitors the workload of participants in the scheme in terms of the number of cases reported. 73% (1,735) of participants reported no cases in 2003, 25% (586) reported between one and four cases and only 2% (43) reported five or more cases. The greatest numbers of cases reported were by HIV/AIDS specialists, one of whom reported 67 cases and another 157. Specialties that had a particularly high level of reporting were paediatric neurologists (PIND) and neonatologists (AIDS/HIV, invasive fungal infections in VLBW infants, tuberculosis in childhood and hyperbilirubuinaemia in the newborn). Community paediatricians continue to make a significant contribution to reporting and their continued involvement in the scheme is highly valued. With the continuation of the PIND, HIV/AIDS and tuberculosis studies, their important contribution will continue in 2004.

Table 2 *Cases reported from June 1986 - December 2003 of conditions under surveillance at June 2003 - (cases confirmed by June 2004 shown in brackets)*

		Reports (confirmed cases)				
Conditions under Surveillance	Date when reporting began	**June 1986-Dec-95**	**Jan 1996-Dec-00**	**2001**	**2002**	**2003**
HIV/AIDS	Jun-86	991 (691)	1017(693)	447 (319)	595 (461)	731 (535)
Congenital rubella	Jun-91	72 (39)	49 (25)	12 (3)	7 (1)	7 (2)
PIND	May-97	— —	1066 (638)	200 (122)	227 (138)	183 (117)
Suspected fatal ADR	Jun-02	— —	— —	— —	8 (5)	8 (3)
Congenital toxoplasmosis *	Jul-02	— —	— —	— —	16 (1)	14 (8)
Severe complications to varicella	Nov-02	— —	— —	— —	29 (14)	159 (93)
Invasive fungal infections	Feb-03	— —	— —	— —	— —	130 (79)
Severe hyperbilirubinaemia	Jun-03	— —	— —	— —	— —	47 (25)
Langerhans cell hystiocytosis	Jun-03	— —	— —	— —	— —	46 (12)
Childhood tuberculosis	Dec-03	— —	— —	— —	— —	50 (25)
Total		**1063 (730)**	**2132 (1443)**	**659 (454)**	**882 (640)**	**1375 (899)**

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

Suspected fatal ADR — Suspected Fatal Adverse Drug Reactions ended in June 2003.

Table 3 *Outcome of follow-up of the cases reported in 2003 of conditions under surveillance at June 2003*

Condition under surveillance	**Date when reporting began**	**Valid reports**	**(%)**	**Invalid reports**			**Not yet known**	**(%)**	**Total**
				Duplicate	**Errors**	**Total(%)**			
HIV/AIDS	Jun-86	2719	(72)	422	502	(24)	138	4	3781
Congenital rubella	Jun-91	70	(48)	25	50	(51)	2	1	147
PIND	May-97	1015	(61)	189	447	(38)	25	1	1676
Suspected fatal ADR	Jun-02	7	(37)	5	6	(58)	1	5	19
Congenital toxoplasmosis*	Jul-02	9	(30)	2	17	(63)	2	7	30
Severe complications of varicella	Oct-02	15	(52)	1	1	(7)	12	41	29
Invasive fungal infections	Feb-03	79	(67)	17	22	(33)	0	0	118
Severe hyperbilirubinaemia	Jun-03	25	(53)	3	19	(47)	0	0	47
Langerhans cell histiocytosis	Jun-03	12	(26)	7	21	(61)	6	13	46
Childhood tuberculosis	Dec-03	25	(50)	6	14	(40)	5	10	50
All		3976	(67)	677	1099	(30)	191	3	5943

*Validation depends on microbiological/pathological details

4 Main findings of studies undertaken in 2003

After 25 months of **congenital cytomegalovirus** (cCMV) surveillance (page 11), 93 confirmed and 71 suspected cases have been reported through the BPSU, with a further 21 reports still being investigated. 20% of cases were identified antenatally. Over 40% of the confirmed cases had neurological signs (microcephaly, seizures, intracranial calcification), and to date there have been seven deaths reported. Parental consent is being sought to retrieve Guthrie cards in order to investigate whether it is possible to confirm or exclude a diagnosis of cCMV using routinely collected neonatal dried blood spot samples.

Surveillance for **congenital rubella** (page 12) has been underway in the UK since 1971. Ten infants born since 1997 have been reported; in six 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 vaccine 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.

The surveillance of **congenital toxoplasmosis** (page 15), which commenced in July 2003, has now been completed, after 24 months. To April 2004 148 suspected cases had been made. Of these, nine cases (one definite, one probable and seven possible) were diagnosed during the study period. Congenital toxoplasmosis accounts for just over half of the children identified with symptomatic toxoplasmosis, although uncertainty remains for some of these children as to whether infection was congenital or acquired postnatally.

The BPSU survey of **HIV and AIDS** (page 17) 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 most reports continue to come from the London area, cases are 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.

Surveillance of **hyperbilirubinaemia in the newborn (>510 micromol/l)** (page 31) commenced in June 2003 and has recently had its surveillance period extended for a second year. 61 reports have been received to April 2004, of which 31 have been confirmed; data on six are still outstanding. 21 of the confirmed cases were male. 25 infants were re-admitted from home for investigation and management of severe jaundice. 20 infants received a total of 22 exchange transfusions. Two infants died for whom, co-morbidity (sepsis) may have been partly responsible.

A 13-month surveillance of **invasive fungal infection in very low birthweight** (page 19) infants commenced in February 2003. There were 88 confirmed cases in the first 12 months of the study. From this it appears that the British Isles has a lower incidence than that seen in the US studies (data from US based on referral series of the sickest babies in tertiary centres). 50% of the cases were under 710grms and 50% of cases were under 25 weeks gestation. Mortality data for 78 of the cases was available, of these 43 were alive at 37 weeks post conception.

Surveillance of **Langerhans cell histiocytosis (LCH)** (page 21) commenced in June 2003 and will continue into 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. In the 11 months since the study commenced 122 cases have been reported of which 26 have so far been confirmed, 13 through the BPSU the remainder through alternate source ascertainment.

Despite the complexity of the conditions involved the survey of **progressive intellectual and neurological deterioration in children (PIND)** (page 24) has proved successful. It is being undertaken to identify any cases of variant Creutzfeldt-Jakob disease (vCJD) in UK children. Over 1,722 cases of suspected PIND have been reported. Among them 716 cases are confirmed diagnoses, consisting of 114 different conditions. Six cases of vCJD have been identified. Active surveillance continues into 2005.

A 13-month surveillance of **severe complications of varicella (chickenpox)** (page 28) came to completion in November 2003. Its primary objective is to estimate the annual incidence of complicated varicella in hospitalised children less than 16 years of age. 188 cases were reported of which 103 have so far been confirmed.

The 13-month survey into **suspected fatal adverse drug reactions (ADRs)** ended in July 2003 (page 31). This prospective study intended to document whether fatal ADRs are a problem in children in the UK. Seven reports met with the case definition. However causality was not confirmed in five of these. In the remaining two cases a causal link was felt only to be a possibility. This study provides no evidence to suggest that there is a major public health problem relating to fatal ADRs in children.

Surveillance of **tuberculosis in childhood** (page 33) commenced in December 2003 for a 13-month period. The study aims to estimate the incidence of tuberculosis in the child population of the British Isles and importantly it will also allow us to validate the enhanced surveillance system currently in place. To April 2004 126 cases have been reported of which 63 have been confirmed to date.

5 Surveillance studies undertaken in 2003

During the year 2003, 13 conditions were the subject of surveillance. Six studies, vitamin K deficiency bleeding (VKDB) (January), thrombosis (February), congenital cytomegalovius (February) internal abdominal injuries due to child abuse (March), suspected fatal adverse drug reactions in childhood (June) and severe complication to varicella (chickenpox) (November) ended. Final reports on VKDB, thrombosis and internal abdominal injuries due to child abuse are contained in the 16th annual report.

Four studies commenced in 2003: invasive fungal infections in very low birth weight infants (February), severe hyperbilirubinaemia (June), Langerhans cell histiocytosis (June) and tuberculosis in childhood (November).

Two studies have commenced in 2004, neonatal herpes simplex virus (January) and medium chain acyl CoA dehydrogenase deficiency (June). Three further studies have been approved, the Sir Peter Tizard bursary submission looking into childhood thyotoxicosis, non-type 1 diabetes and early onset eating disorders (5-13 years). These studies will commence once MREC and funding approval have been secured.

The data described in the following reports were correct at the time of submission. Data are continually being updated and will be reported in future BPSU annual reports or quarterly bulletins.

On behalf of all the investigators the BPSU would like to thank all those who reported cases and contributed data to studies undertaken by the BPSU.

Table 4 *Studies underway in the year 2003/4*

Page	Study	Principal Investigators	Research Institution
11	Congenital cytomegalovirus	P Tookey,	ICH (London)
12	Congenital rubella*	P Tookey, C Peckham	ICH (London)
15	Congenital toxoplasmosis*	R Gilbert, M Stanford	ICH (London), Kings College Hospital
17	HIV/AIDS in childhood *	P Tookey, A Nicoll, D Goldberg	ICH (London), HPA, SCIEH
19	Invasive fungal infections in VLBW infants	W McGuire, L Clerihew	Ninewells Hospital
21	Langerhans cell histiocytosis*	L Parker, J Salotti, V Naduri, R Lynn	RVI Newcastle, GOS, BPSU
24	Progressive intellectual and neurological deterioration *	C Verity, G Devereux, L Stellatano, A Nicoll, R Will, AM Winstone	Addenbrookes Hospital, HPA, CJDSU
28	Severe compications of varicella	C Bramley	SCIEH
30	Severe hyperbilirubinaemia*	D Manning	Arrowe Park Hospital
31	Suspected fatal adverse drug reactions	K Cheng, T Stephenson	Medicines Control Agency, QMC Nottingham
33	Tuberculosis in childhood*	D Shingadia, S Teo	Royal London Hospital

*Studies still in progress as of July 2004

Congenital cytomegalovirus (cCMV)

Key points

- **Ninety-three infants with confirmed and 71 with suspected congenital CMV were reported over a two-year period.**
- **Study enrolment is now closed, although information on any of the 21 outstanding reports would still be welcome.**
- **Follow up information to establish the health status of surviving children between the ages of 16 and 30 months has been sought from notifying paediatricians and is currently being collated.**
- **Parental consent is being sought to retrieve Guthrie cards in order to investigate whether it is possible to confirm or exclude a diagnosis of cCMV using routinely collected neonatal dried blood spot samples.**

Background

Congenital cytomegalovirus (cCMV) appeared on the orange card for 25 months from February 2001 to February 2003. Notification of infants with suspected or confirmed cCMV born in 2001 and 2002 was sought. It was expected that congenitally infected infants who were asymptomatic at birth or had non-specific symptoms would be unlikely to be identified or reported.

Primary or recurrent maternal CMV infection in pregnancy can result in fetal infection. Although most infants have no associated problems, cCMV can cause neonatal death or severe disease and long-term disability in 10-20% of infected children. Incidence of cCMV ranges from 0.3% to 2% of all live births worldwide; earlier British studies suggest an incidence of 3-4/1000 live births, but this varies in different population groups and may have changed over time. Congenital infection can only be confirmed on the basis of samples collected in the first three weeks of life and detection of CMV in later samples is likely to reflect infection acquired at delivery or postnatally, which is common, but rarely associated with adverse outcome.

In Britain about 20% of children become infected by 12 months of age[1]. About 10% of congenitally infected infants are symptomatic at birth and most of these have long-term complications, for example cerebral palsy, mental retardation and sensorineural hearing loss (SNHL). In contrast, most asymptomatic infants develop normally although a minority have neurological sequelae, usually SNHL.

Objectives

The study was established to ascertain the population prevalence of clinically recognised congenital CMV infection in infants born in the British Isles, current management strategies and the clinical disease outcome.

The enrolment period has now ended and follow-up information is currently being requested from notifying paediatricians for reported children in their second or third year of life.

We also wanted to explore the feasibility of using routinely collected neonatal dried blood spots to confirm or exclude a diagnosis of congenital CMV infection in infants who present after three weeks of age. We are currently seeking parental consent (through the notifying paediatrician) to retrieve the Guthrie cards for this aspect of the study.

Surveillance Period

February 2001 - February 2003 (inclusive).

Case Definition

Any infant with confirmed or suspected cCMV infection born in the UK or Ireland between 1st January 2001 and 31st December 2002.

Confirmed cases: any infant with cCMV infection, confirmed by PCR or virus isolation from urine, blood, saliva or tissue taken at biopsy within three weeks of birth.

Suspected cases: any infant with symptoms compatible with cCMV infection aged under 12 months with CMV isolated from urine, blood, saliva or tissue taken at biopsy after three weeks of age, and/or with CMV specific IgM after three weeks of age.

Table 5 *Reports made through the BPSU to March 2003*

	Confirmed	Suspected	Duplicates or errors	Outstanding	**TOTAL**
England	77	62	76	17	**232**
Wales	2	2	5	2	**11**
Scotland	8	5	11	1	**25**
NI	1	1	4	0	**6**
RoI	5	1	7	1	**14**
TOTAL	**93**	**71**	**103**	**21**	**288**

Analysis

During the 25-month study period (February 2001-February 2003) 288 reports were received from 224 paediatricians. These reports yielded 93 (32%) confirmed cases (with laboratory confirmation of infection in first three weeks of life) and 71 (25%) suspected cases (laboratory confirmation of infection only available from samples taken when the infant was over 21 days old). The 103 duplicate or error reports included 37 infants with confirmed or suspected infection who were born outside the study period. 21 reports are still outstanding, and may not now be classified (Table 5).

We had expected that in the absence of widespread routine testing, most infants reported would be symptomatic. However about 20% of the 93 infants with confirmed cCMV were investigated and identified because of maternal or fetal signs or symptoms in the antenatal period. Among the other 80%, about half presented with neurological symptoms and half had non-specific signs neonatally, for example, small for gestational age, jaundice, hepatosplenomegaly. Almost a quarter of the confirmed cases were treated with ganciclovir. Eight of the 93 infants (9%) are known to have died, all of whom were symptomatic neonatally.

We appreciate the support of paediatricians in notifying cases, completing forms, and forwarding information to parents seeking consent for the retrieval of Guthrie cards. Full study findings for both confirmed and suspected cases, and an assessment of the feasibility of using the neonatal dried blood spots for retrospective diagnosis of cCMV, will be reported subsequently.

Ethics Approval

This study has received approval from GOS Hospital for Children NHS Trust/Institute of Child Health Research Ethics Committee.

Funding

This study is funded from departmental resources.

Support Group

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Reference

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Congenital Rubella

Key Points

- **Since 1997 only 10 congenital rubella births have been reported in the UK.**
- **Six of 10 congenital rubella births were imported infections, with maternal infection acquired abroad although the infant was born in the UK.**
- **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.**

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 an average of 22 births and 54 terminations a year in 1986-90. Active surveillance through the BPSU started in 1990.

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 2003 the recorded uptake for 2 year olds was only 81%[1]. This is not sufficient for the long-term maintenance of herd immunity levels of 85-88%, which are required to prevent circulation of rubella infection, particularly since few children now acquire natural infection. It is possible that rubella could once again start to

Table 6 Congenital rubella reports to BPSU 1990-2003
(includes births occurring in earlier years)

	Registered cases	Already reported	Outstanding	Duplicate, error or lost	Total
England, Scotland and Wales	52	11	0	65	128
Ireland (all)	4	2	1	8	15

circulate in the UK, as it does in many other parts of the world. The World Health Organisation Regional Office for Europe has set a target of less than one congenital rubella syndrome case per 100,000 births by 2010, and identified sub-optimal MMR coverage and migration within Europe as being among the challenges to this target [2]. Awareness of rubella infection and congenital rubella among paediatricians and health professionals looking after pregnant women 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 in England, Scotland and Wales and investigating the circumstances surrounding any new cases.

Surveillance Period

Surveillance began in January 1990 and is reviewed annually.

Case Definition

Any 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. Reports of stillbirths associated with congenital rubella infection are also requested.

Analysis

BPSU notifications: There were seven notifications of congenital rubella to the BPSU in 2003. Only two of these reports were confirmed cases: one was imported, the mother having acquired the infection in Africa, and the other infant was born to a woman who was born abroad but acquired her infection in the UK. One notification was a duplicate, and four were reporting errors (including one infant with CR who was born in Southern Asia).

Since active surveillance began in 1990, 143 reports have been made through the BPSU (Table 6). Of the 128 reports from England, Scotland and Wales, 48 are confirmed or compatible, previously unreported cases of congenital rubella, four are possible cases, and 11 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. Fifteen reports were from Ireland and Northern Ireland, and included three children with confirmed congenital rubella (one born in 1989 and two in 1996), and a fourth possible case (born in 1983). One report from Ireland is currently outstanding.

Congenital rubella 1990-2003: Fifty-five children with confirmed or compatible congenital rubella have been born and reported since the beginning of active surveillance in 1990 and 41 of these (75%) were first reported through the BPSU (Table 7). 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

Table 7 Confirmed and compatible congenital rubella births reported to the NCRSP 1971-2003*
(England, Scotland & Wales only)

	Primary source of notification		
Year of birth	BPSU	Other	Total
1964-69	0	39	39
1970-79	1	453	454
1980-89	13	320	333
1990-2003~	41	14	55*
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	9	3	12
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
Total	**55**	**826**	**881**

* The data for recent years are provisional
~ The data for 1990-2003 include 2 reported stillbirths
** Includes a set of triplets

UK, had only arrived in the country relatively recently [3,4]. Three women had confirmed reinfection in pregnancy. There have also been 75 terminations for rubella disease or contact in pregnancy recorded by ONS in England and Wales during the period 1990-2002 [5].

Recent Reports:

Ten infants with congenital rubella were born and reported between 1999 and 2003 (Table 7). Six were imported cases with maternal infection acquired abroad (three in Southern Asia, three in Africa). Four infants were born to women whose infection was acquired in the UK. One British-born woman acquired rubella in Scotland, although the infection was epidemiologically linked to an outbreak in Greece in 1999[6]. 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 lived 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[7]. Women who have come to the UK from countries without comprehensive and long-standing vaccination programmes are likely to be at higher risk if there is renewed circulation of rubella virus in the UK. Even while rubella infection is rare in the UK, 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. Please notify to the BPSU all infants with suspected congenital rubella who were born in the UK or Ireland, whether or not they have the associated typical defects. We are extremely grateful to all participating paediatricians, especially those who have notified cases and completed questionnaires.

Ethics Approval

This study has approval from GOS Hospital for Children NHS Trust/Institute of Child Health Research Ethics Committee.

Funding

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

Support Group

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Congenital toxoplasmosis

Key Points

- **Congenital toxoplasmosis accounts for just over half (14/27) of the children identified with symptomatic toxoplasmosis, although uncertainty remains for some of these children as to whether infection was congenital or acquired postnatally.**
- **Multiple sources of case ascertainment are important for the surveillance of congenital toxoplasmosis**
- **After the study ends in August 2004, we may be able to further refine classification of congenital or acquired infection for some children using results from retrospective testing of stored Guthrie card blood.**

Background

A national surveillance study of toxoplasma infection in children began in August 2002. The study utilises three reporting sources: the BPSU, The British Ophthalmic Surveillance Unit, (BOSU) and toxoplasma referral laboratories in the UK and Ireland. The primary aim of the study is to determine the birth prevalence of symptomatic congenital toxoplasmosis. Extrapolation from studies in countries with a similar seroprevalence of infection in pregnancy suggest that the birth prevalence is about 1 in 10,000 live births or about 70 births in the UK per year[1]. We expect approximately 5-10% of congenitally infected children to present with symptoms (up to seven children in the UK) based on cohort studies of children with congenital toxoplasmosis[1]. Congenitally infected children need to be differentiated from the much larger number of children who acquire toxoplasmosis after birth, some of whom develop ocular signs and symptoms that are indistinguishable from congenital toxoplasmosis. The incidence of infection in childhood has been estimated to be 2.6 times higher (95%CI: 1.6, 4.2) than the incidence in the child-bearing age group (incidence 1.5/1000 susceptibles /year in women of childbearing age: 95%CI: 0.7, 2.7)[2]. Consequently, children are an important group for primary prevention of toxoplasma infection. There is a lack of information on how most children acquire infection or whether they share the same risk factors as for pregnant women namely undercooked meat and oocysts in contaminated soil or water[3]. The risk of symptomatic ocular disease after acute acquired toxoplasmosis has been estimated to be about 1% but few data are available for childhood[4].

Objective

To determine the incidence of symptomatic congenital toxoplasmosis in childhood, and its clinical presentation and severity.

Surveillance Period

July 2002 to July 2004 (inclusive).

Case Definition

Paediatricians are asked to report any child (<16 years) or stillbirth with suspected congenital toxoplasmosis. This reporting definition includes any child: (a) under 2 years with toxoplasma-specific IgM,IgA or IgG antibodies (after this age IgM or IgA may reflect acquired infection), or (b) children with hydrocephalus, intracranial calcification, microcephaly, retinitis, microphthalmia or unexplained hepatosplenomegaly and lymphadenopathy in infancy. Ophthalmologists are asked to report any newly diagnosed children suspected to have

Table 8 *Reports of suspected congenital toxoplasmosis in childhood by reporting source (by April 2004)*

	No of cases notified	No of questionnaire received	No of outstanding questionnaire	No. of mis-notification
Primary Sources				
BOSU	54	28	15	11
BPSU	33	23	3	7
*Referral Labs**	48	48	0	0
** *Individuals*	3	1	2	0
Primary Sources SubTotal:	138	100	20	18
*Secondary Sources	10	5	3	2
Total	**148**	**105**	**23**	**20**

** No response fromInverness, or Dublin laboratories*
*** Case notification received from individual clinician seeing child with suspected CT 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.*

congenital toxoplasmosis including any child with unexplained retinochoroiditis or other ocular findings consistent with congenital toxoplasmosis. Reference laboratories have been asked to report any clinical samples referred for testing that meet the above criteria for paediatricians and ophthalmologists.

Analysis

By April 2004, 148 reports of suspected toxoplasmosis had been made. 33 (22%) were initially notified through BPSU, 54 (36%) through BOSU, 48 (32%) through the reference laboratories, three through individual clinicians reporting direct to the study and 10 (7%) through secondary sources who were clinicians approached for further information after an initial report by a laboratory, paediatrician or ophthalmologist (Table 8). To date, completed questionnaires have been received on 105 of the 148 reports (71%). There were 20 notification errors (13%) and 23 questionnaires (15%) remain outstanding. Most reports were through BOSU, and the Toxoplasma Reference Laboratory in Swansea.

Table 9 *Sources of Patients*

Source	No. of Patients
BOSU alone	25
BPSU alone	17
Reference Lab alone	41
Individual	1
BOSU + BPSU + Reference Lab	1
BOSU + Reference Lab + Secondary sources	2
BPSU + Reference Lab	3
BPSU + Secondary sources	2
Reference Lab + Secondary sources	1
Total number of patients	**93**

Table 9 shows which sources reported the total of 93 children with suspected symptomatic toxoplasma infection, of which 51 presented within the surveillance period of the study, and the remainder were cases newly diagnosed prior to the start of the surveillance period. Provisional classification, based on the clinical and laboratory findings and the clinician's opinion, 27 (53 %) were classified as definite or probable toxoplasma retinitis and/or congenital toxoplasmosis. All were live births. Further information from clinicians and, in some cases, from retrospective testing for specific IgM of stored neonatal Guthrie card blood spots, may modify these classifications. Just over half of the children were considered to have congenital toxoplasmosis (14/27; 52%), and 23 (85%) had toxoplasma retinitis. Four had no information on ocular findings. As expected, most children with congenital toxoplasmosis (10/14; 71%) presented in the first year of life, but two presented with ocular symptoms in adolescence and were considered to have congenital toxoplasmosis due to the presence of intracranial pathology. In the 22 children with toxoplasma retinitis 13 (59%) did not have evidence of congenital toxoplasmosis, and all 13 presented at or after three years of age and were most likely to have acquired infection after birth. In addition to these 27 cases of toxoplasmosis, a further six – either miscarriages or stillbirths- were reported, five classified as possible and one as definite congenital toxoplasmosis.

Funding

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HIV/AIDS infection in childhood

Key points

- **Reports of infants born to HIV infected women have increased substantially in recent years, with the largest increase in 2003, but the proportion of infants born to HIV infected women and who are themselves infected is declining.**
- **In spite of greatly improved antenatal detection rates, infants born in the British Isles to undiagnosed women continue to present with symptomatic HIV infection.**
- **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. Follow up of uninfected children to identify any possible adverse effects of exposure to prophylactic antiretroviral therapy is being established.**

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 acquired their infection through mother to child transmission. 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 these 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[2]. Unlinked anonymous survey data[3] indicate that the number of births to HIV infected women (both diagnosed and undiagnosed) has increased substantially in the UK from about 300 in 1997 to nearly 700 in 2002. The proportion of women diagnosed before delivery increased from an estimated 32% to at least 79% over the same period[3] and there has been a marked decline in the proportion of HIV infected infants.

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.

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.

Analysis

Number of reports: By the end of December 2003 there had been 3,568 reports through the BPSU, of which 2,430 were confirmed cases of HIV infection or infants at risk of vertical transmission, 494 were duplicates and 494 were reporting errors; the remaining 198 reports were still being investigated. A further 2,505 confirmed cases were reported through other notification sources; these include paediatric reports made directly to the NSHPC (mainly from a small number of major units), 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, CDSC and the Scottish Centre for Infection and Environmental Health, and children reported through the UK Haemophilia Centre. Table 10 shows the likely source of infection or exposure for all confirmed reports.

Children born abroad: 542 (11%) of all 4,935 children ever reported in the UK and Ireland were born abroad and about 95% of these are known to be infected. 302 (56%) of the 542 children born abroad have been notified since 2000 and more than two thirds of these were at least five years old when first seen: 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 was unknown.

Table 10 HIV infection and infants born to HIV infected women (all reporting sources) (notified by 31 December 2003)

Exposure / likely source of infection	BPSU reports	Reports from other sources	**Total**
Born to HIV infected woman	2336	2238	**4574***
Haemophilia treatment	48	219	**267**
Blood transfusion/products	33	19	**52**
Other/not yet established	13	29	**42**
Total	**2430**	**2505**	**4935**

*: 1,115 known to be infected – see Table 11.

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. Enhanced follow-up information for approximately 75% of infected children is currently collected through the Collaborative HIV Paediatric Study (CHIPS), a collaboration between the NSHPC, the MRC Clinical Trials Unit and the centres involved in PENTA treatment trials.

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 and we are now establishing on-going, consented follow up of children exposed to ART (CHART study), 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, CDSC HIV and STI Division.

Children born to infected women: Reports of children born to HIV infected women have increased substantially in recent years: of the 4,574 (Table 11) children ever reported, more than 1,000 were reported in 2003. By the end of December 2003, 1,115 children were known to be infected, and 2,404 uninfected. 11% 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.

Table 11 Infection status of children born to HIV infected women (including children born abroad) (notified by 31 December 2003*)*

Region of first report	Infected	Indeterminate	Not infected	**Total**
London	710	570	1356	**2636**
Rest of England	275	254	494	**1023**
Wales & Northern Ireland (NI)	13	15	16	**44**
Scotland	50	36	198	**284**
Ireland	67	180	340	**587**
Total	**1115**	**1055**	**2404**	**4574**

4,069 (89%) vertically exposed children reported by the end of 2003 were born in the British Isles (Table 12) and 2,321 (57%) of these were born between 2000 and 2003. An additional 294 births in this latter period were reported in the first three months of 2004. This dramatic increase in notifications largely reflects the improvement in antenatal diagnosis rates, and the majority of infants born to these diagnosed women will themselves be uninfected. Twelve of the 26 children born since the beginning of 2002, with infection confirmed by the end of 2003, were born to undiagnosed women and all but one of the 12 had HIV symptoms at presentation.

Table 12 Year of birth and infection status of children born in the UK and Ireland to HIV infected women. (*notified by 31 December 2003)*

Year of Birth	Infected	Indeterminate	Not infected	**Total**
Pre 1992	168	58	241	**467**
1992-93	112	33	103	**248**
1994-95	96	39	116	**251**
1996-97	105	32	186	**323**
1998-99	76	36	347	**459**
2000-01	64	164	771	**999**
2002-03	26	683	613	**1322**
Total	**647**	**1045**	**2377**	**4069**

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 SCIEH Weekly Report (Scotland) (available at www.show.scot.nhs.uk/scieh).

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 and diligence.

Ethics Approval

The London Multicentre Research Ethics Committee has reviewed and approved the NSHPC and the associated CHIPS study.

Funding

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Support Groups

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Invasive fungal infection in very low birthweight infants

Key Points

- **There were 88 confirmed cases in the first 12 months of the study. From this it appears that the British Isles has a lower incidence than that seen in US studies.**
- **This is a disease of the smallest and most preterm infants whose median birthweight was 710g and median gestational age at birth was 25 completed weeks.**
- **Mortality data for 78 of the cases was available, of these 43 were alive at 37 weeks post conception.**

Background

Nosocomial invasive fungal infection, most commonly due to *Candida spp*., is an increasingly common cause of morbidity and mortality in preterm infants cared for in the neonatal intensive care setting[1, 2]. The increase in incidence over the past 20 years is likely to be due to the improved survival rates of very immature infants, and the invasive and intensive nature of the care that these infants need. The estimated incidence of invasive fungal infection in very low birth weight infants (VLBW: birth weight <1500 g) is about 2%[2,3]. In extremely low birth weight infants (ELBW: birth weight <1000 g), the incidence has been estimated to be as high as 10% [4]. However, these estimates are based on limited case-series from tertiary centres in North America, and may have been affected by referral and ascertainment biases.

In neonatal intensive care units, systemic candidal infection accounts for about 10% of all cases of sepsis diagnosed in infants more than 72 hours old. The estimated attributable mortality of about 25% is much higher than that associated with invasive bacterial infection[2,3]. The clinical presentation of invasive fungal and bacterial infection is similar. In addition to fungaemia, infants may present with pneumonia, meningitis, renal tract infection, ophthalmitis, osteomyelitis, endocarditis, and skin abscesses. The diagnosis may be delayed due to an inability to recover consistently the organism from blood, cerebro-spinal fluid (CSF), or urine[5].

Objectives

The aim of the study is to:

- determine the incidence of invasive fungal infection in very low birth weight infants.
- describe the patterns and clinical spectrum of presentation.
- determine which fungi are responsible (including anti-fungal resistance patterns).
- elicit current treatment strategies.
- describe clinical outcomes at 37 weeks post gestational age.

Given the high mortality, and the difficulty in establishing an early diagnosis, there is a need to assess the effect of strategies to prevent invasive fungal infection in VLBW infants[6]. The evaluation of such measures would be assisted by the availability of national epidemiological data in an unselected population of VLBW infants.

Surveillance Period

February 2003-February 2004 (inclusive).

Case Definition

Live born VLBW infant with confirmed invasive fungal infection as determined by one or more of the following:

- culture from a sterile site:
  - o CSF
  - o blood (from peripheral sites, not from indwelling catheters)
  - o urine (obtained by sterile urethral catheterisation or supra-pubic bladder tap)
  - o bone or joint
  - o peritoneal or pleural space
  - o central venous line tip
- pathognomonic findings on ophthalmological examination
- pathognomonic findings on renal ultrasound examination
- autopsy diagnosis

Analysis

Eight-eight confirmed cases of invasive fungal infection in VLBW (<1500g) infants were identified during the first twelve months of the study, (estimated incidence of 10 per 1000 live births). The median birth weight was 710 grams (range 420g – 1,460g). Seventy-six (86%) of the infants were of extremely low birth weight (<1000g), an estimated incidence of 22 per 1000 live births. Median gestational age at birth was found to be 25 weeks (range 22-32 completed weeks) Candida was isolated in 98% of cases - *Candida albicans* in 47(53%) of cases, and *C. parapsilosis* in 17(19%). The organisms were isolated from blood in 67(76%) of cases, central line tips in 37(42%), and urine in 23(26%). Six infants (7%) had evidence of meningitis. Thirty-five (40%) of cases had received prophylactic antifungal therapy. The antifungal treatment regimens used were: amphotericin B 15(17%); liposomal amphotericin 60(68%); fluconazole 41(47%); flucytosine 27(31%). Fifty -three (60%) infants received more than one antifungal agent. We have identified one case of drug resistance. Forty-three of the 78 infants (55%) for whom outcome data were available were alive at 37 weeks post-gestational age. All cause mortality was estimated at 45%.

The majority of cases occurred in ELBW infants, suggesting that preventative strategies should be focused on this population. Short-term mortality was high, which is important in the counselling of parents. Fungal isolates, predominantly Candida species, were most commonly from the bloodstream and urinary tract. Isolation of antifungal drug resistant strains from these infants is rare.

Ethics Approval

This study has been approved by the Scottish MREC.

Funding

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Figure 4 *Infant undergoing treatment for invasive fungal infection*

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Langerhans Cell Histiocytosis (LCH)

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 (LCH), previously known as Histiocytosis X, is a disease in which cells with the characteristics of epidermal Langerhans cells accumulate in various parts of the body and cause tissue damage by the release of cytokines[1]. Langerhans cells are normally found only in the skin, lymph nodes, and main airways. In disease, LCH commonly affects skin (rash), bone (single or multiple lesions) and the pituitary gland (causing diabetes insipidus) and may also affect the lungs, intestines, spleen, and bone marrow. The cause of LCH is unknown and it does not appear to be related to infection, cancer or hereditary. It may be triggered by an unusual reaction of the immune system to something commonly found in the environment.

It occurs more commonly in childhood than adulthood and tends to be more severe in very young children, when several organs may be affected[2]. Around 10-20% of patients, usually infants, die. Not all children require treatment and, in many patients, the disease eventually spontaneously regresses. However, there may be long term sequelae due to damage caused by the disease process, e.g. intellectual problems, endocrine abnormalities and orthopaedic disabilities[3]. Quality of life in survivors is often poor and chronic sequelae are a constant drain on health care resources[4].

It is estimated that one in 200,000 children are affected each year. Over 75% of

Figure 5a *Plain X ray showing a lytic lesion of the humerus*

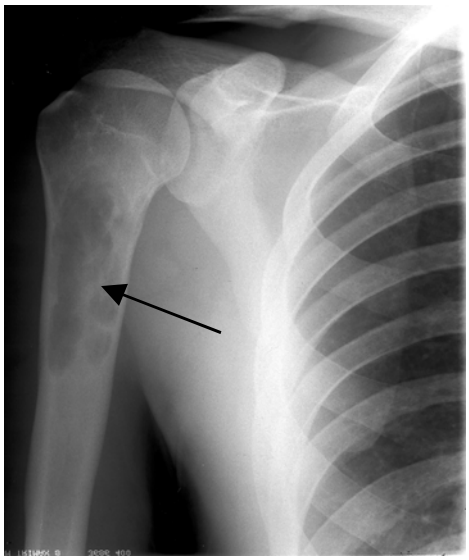


Figure 5b *Skull X ray showing the characteristic multiple lytic lesions of LCH*

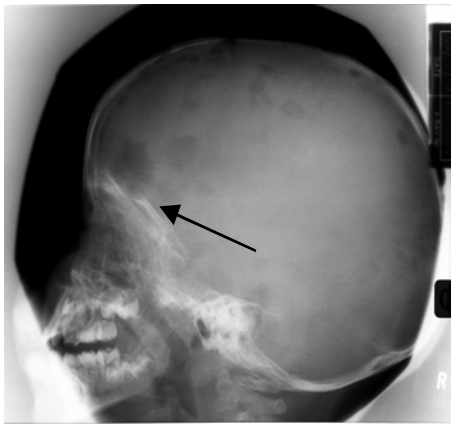


Figure 5c *Chest X-ray demonstrating diffuse interstitial shadowing in the acute phase of LCH*

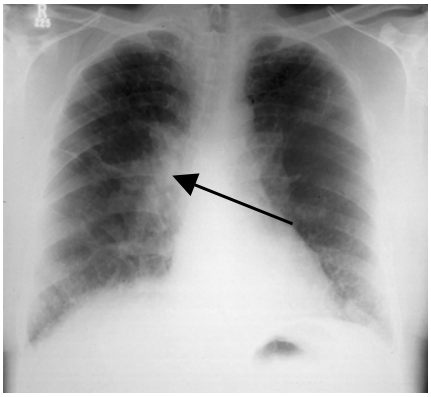


Figure 5d *Rash resembling seborrhoeic dermatitis in scalp*

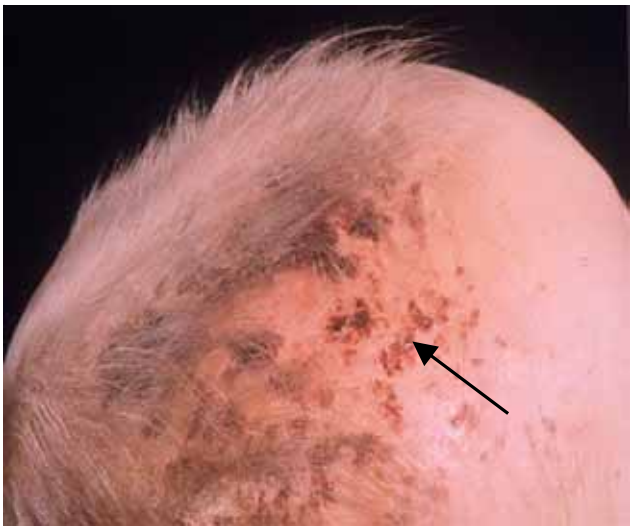


Figure 5e *Post-auricular rash*

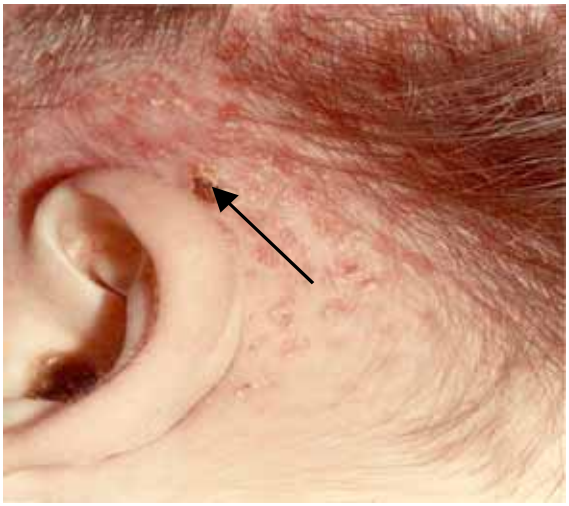
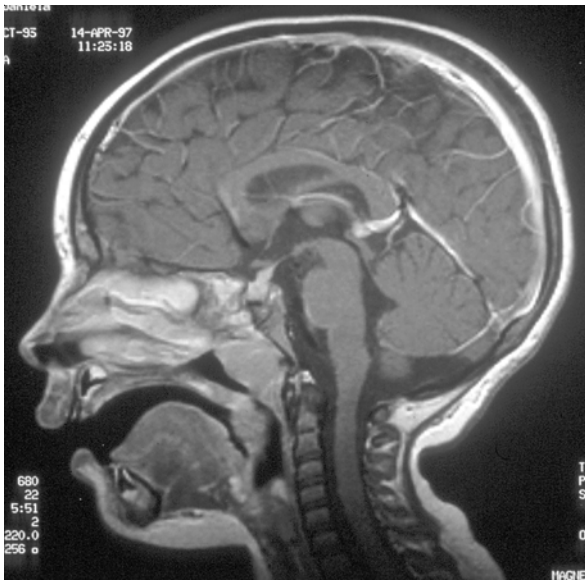


Figure 5f *MRI showing pituitary involvement*



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) has been reported for Denmark, during the 1980's[5]. Delay in diagnosis often limits access to appropriate treatment. This suggests an estimated 50 -100 new cases per year in children in the UK which has a childhood population of around 13 million.

Since July 2003, paediatricians have been reporting children newly diagnosed with LCH through the BPSU monthly orange card system. In addition, cases have also been notified via a six-monthly mailing to other clinicians including pathologists, oncologists, dermatologists, radiologists, endocrinologists, nephrologists, rheumatologists and orthopaedic and paediatric surgeons, by the study team at Newcastle. The disease takes many forms and clinicians who are not paediatricians or members of the RCPCH may see cases. A third source has been the United Kingdom Children's Cancer Study Group (UKCCSG) who register cases of LCH.

Objectives

The aim of this study is to

- describe the epidemiology of LCH in the UK and Ireland

In particular, to

- describe the incidence of LCH by age, sex, and extent of disease at diagnosis
- assess the frequency of familial LCH
- document patterns of presentation e.g. interval between the onset of symptoms and diagnosis
- study variation between ethnic groups
- describe regional differences in incidence rate, e.g. north/south or urban/rural

Surveillance Period

June 2003 – June 2005 (inclusive).

Case Definition

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
i) because clinical features suggest spontaneous resolution or

ii) because the risk of the biopsy procedure in view of the location of the lesion (e.g. cervical vertebra, pituitary mass), is considered too great.

Clinical features of LCH

Bony lesions present with: bony swelling (e.g. skull lesion) with/without overlying soft tissue swelling; proptosis; lytic bone lesions: skull, long bones, ribs, scapula, pelvis; vertebral collapse, wedge compression (Figures 5a, 5b).

Lung Involvement: Interstitial pneumonitis; pneumothorax (Figure 5c)

Skin involvement: rash resembling seborrhoeic dermatitis on scalp (Figure 5d); post auricular rash (Figure 5e); rash in flexures e.g. severe nappy rash and maculopapula rash on trunk.

Hypothalmic – pituitary involvement (Figure 5f): diabetes insipidus, anterior pituitary deficiency; hypothalamic dysfunction e.g. binge eating, temperature instability, obesity.

Other: recurrent otitis with otorrhea; colitis presenting as diarrhoea, blood in stools, protein-losing enteropathy; liver dysfunction, sclerosing cholangitis; bone marrow involvement with pancytopenia.

Preliminary Analysis

Number of reports: In the 11 months since the study began, 67 cases have been notified to the BPSU and 55 notified through Newcastle mailing (NCL). A third of these reports have been found subsequently to be mis-reports including cases diagnosed outside the study period, adult cases, and cases where the diagnosis has subsequently changed. Another third of questionnaires are still outstanding and reminders have been posted (Table 13).

The UKCCSG has been used to reconcile the number of reported cases but no questionnaires have been sent out through the system. Only three cases have so far been identified through the UKCCSG but not reported through either the BPSU or Newcastle systems (Table 14).

The UKCCSG registered 30 new cases of LCH in 2003 but the average number of cases registered in the previous 10 years was 37. It is also important to note that the UKCCSG has details of 90-95% of all UK and Irish childhood cancers and therefore may not provide the full numbers of LCH cases. On this basis further cases may be expected.

It was anticipated that between 50-100 cases would be notified over a two-year period based on the estimated incidence in Denmark (5.4 per million) in the 1980s. Our projected figure from reports so far will be approximately 52 and the UKCCSG data suggests that there could be up to 80 cases. Based on this study data, the national incidence rate is estimated to be two per million children in the UK and using UKCCSG figures the estimate would be 3 per million.

Table 14 Method of ascertainment of confirmed cases

Notification method	Cases
Both BPSU/NCL	6
BPSU only	13
NCL mailing only	2
UKCCSG registry only	3
Total	**24**

A further year of surveillance is anticipated to allow confirmation of these estimates and to provide sufficient numbers to identify patterns of presentation and delays in diagnosis.

Preliminary observations

Of the 24 confirmed cases, there are 14 male and 10 female. The average age at diagnosis was 5.4 years. 75% of cases have single system involvement (skin or bone); one patient, aged one month, has died; one patient has Trisomy 3 and another has medulloblastoma.

We will report a more complete set of clinical observations in future reports.

Table 13 All reports of cases of LCH by source of notification, July 2003-April 2004

	No. of questionnaires sent	No. of reports confirmed	No. of outstanding questionnaires	No. of mis-reports
BPSU	67	28	20	19
Newcastle	55	13	21	21
Total	**122**	**41**	**41**	**40**

Excluding duplicates, this has resulted in 24 confirmed cases from all sources.

Ethics Approval

This study has been approved by the London MREC.

Funding

The Histiocytosis Research Trust.

Support Group

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Progressive Intellectual and Neurological Deterioration in UK children

Key points

- **Further active surveillance is planned until April 2005.**
- **Even if you have made a diagnosis we still want to hear about all children with progressive intellectual and neurological deterioration. This is important because we want to ensure that ascertainment is as complete as possible.**
- **Six cases of variant Creutzfeldt-Jakob disease (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.**
- **Over the seven-year study period 1,722 children have been reported. 1,234 cases have been discussed by an expert neurological advisory group of six paediatric neurologists. 716 have a definite diagnosis which is not vCJD, and these comprise 114 known degenerative conditions.**
- **There are districts that report relatively large numbers of cases of progressive intellectual and neurological deterioration (PIND). In some of these areas there are high consanguinity rates and a heterogeneous mixture of diagnoses[1].**

Background

Active prospective surveillance of UK children with progressive intellectual and neurological deterioration (PIND) commenced in May 1997. It is funded by the Department of Health and 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)[2]. Variant CJD has been described in patients as young as 12 years of age[3] and it could occur in even younger children. The presentation of vCJD is not typical of classical CJD and it is possible that a different variant of CJD might occur in children. The strategy is to detect suspected vCJD cases by looking at a broader group of conditions causing PIND. In this way not only are vCJD cases detected, but also unique epidemiological data on a variety of PIND conditions are obtained[4].

The surveillance co-ordinators use a detailed questionnaire to gather information via a telephone interview or site visit to review the case notes. An expert neurological advisory group consisting of six paediatric neurologists supports the surveillance team by meeting quarterly, discussing all newly notified anonymised cases, and classifying them according to study categories. 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 – progressive intellectual and neurological deterioration (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.

Case Definition

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.

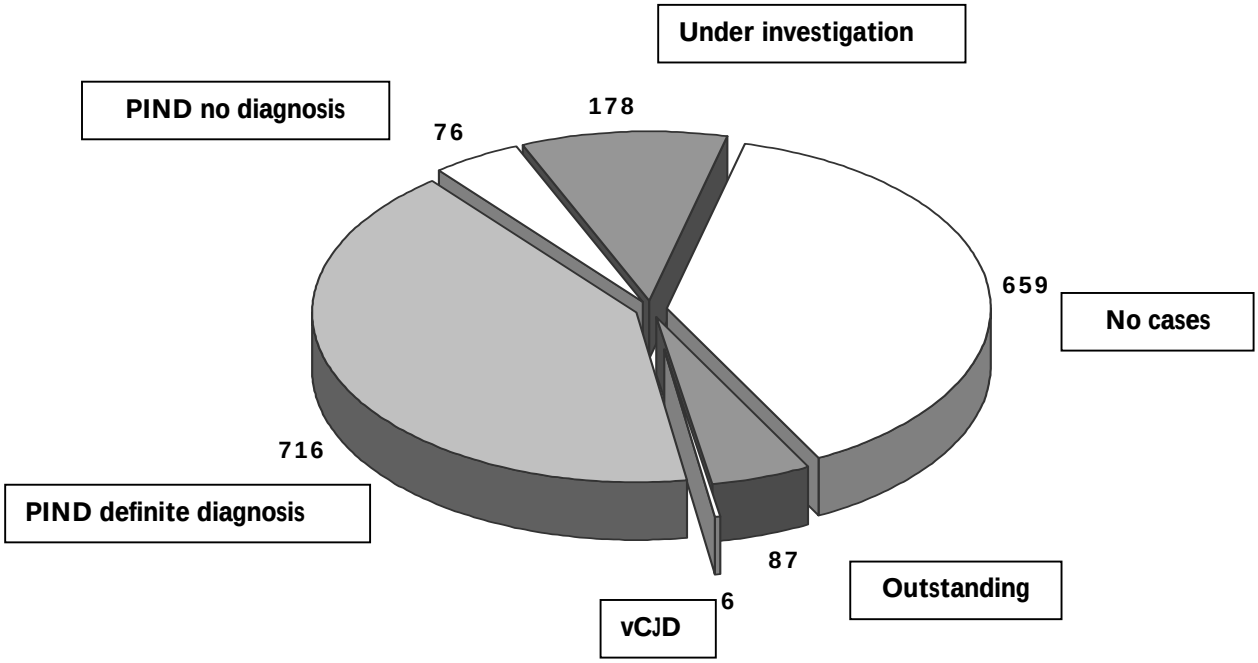
Reports restricted to: Cases seen in the last month but including those whose conditions began earlier (i.e. including "old cases" of children in follow-up (if seen in that month).

Analysis

By the end of April 2004 a total of 1,722 children had been reported via the BPSU (Figure 6). There were 716 children with PIND and a definite underlying diagnosis, 76 in whom no diagnosis had been made and 178 who were still under investigation. There were 659 "No Cases" that included those who did not fulfil the criteria for PIND, reporting errors and duplicate reports. There were 87 outstanding cases that include nine cases due for discussion at the July 2004 Expert Group meeting and 78 awaiting data collection. Details about the six cases of either definite or probable vCJD are given below.

Definite or probable cases of vCJD: Six cases of vCJD have been identified – four females and two males. The youngest was a female aged 12 years at onset. The other female cases were:

Figure 6 *PIND study – current status*



one aged 13 years and two aged 14 years at onset. Both males were aged 15 years at onset. One case was reported in 1998, two in 1999, one in 2000 and two in 2001. All six cases have died and neuropathology has confirmed vCJD in four of them (fulfilling the "definite" case classification). Two died without neuropathological confirmation (fulfilling the "probable" case definition).

PIND children who have definite 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 disease or a likely underlying diagnosis that is not vCJD. In the 716 children with a confirmed diagnosis other than vCJD there were 114 different neurodegenerative conditions. The six most commonly occurring diagnoses are shown in Figure 7.

Variation in reporting by district: Geographical analysis by hospital of report and by residence reveals significant variations. A number of 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 (213 cases) followed by North East Thames (195 cases) and West Midlands (185 cases).

Variation in reporting by category of referring paediatrician: Most cases were reported by general paediatricians (604 - 35%) followed by paediatric neurologists (528 - 31%) then community paediatricians (387 - 22%) (Figure 8).

Figure 7 *Six most commonly reported PIND diagnoses*

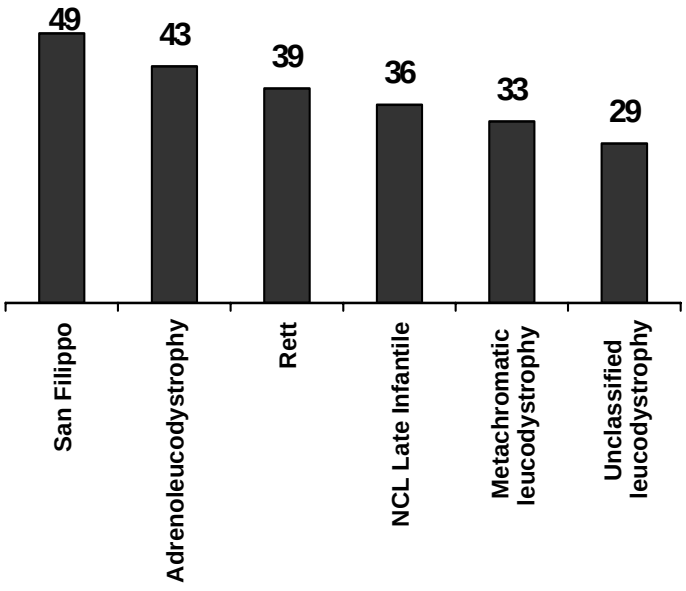
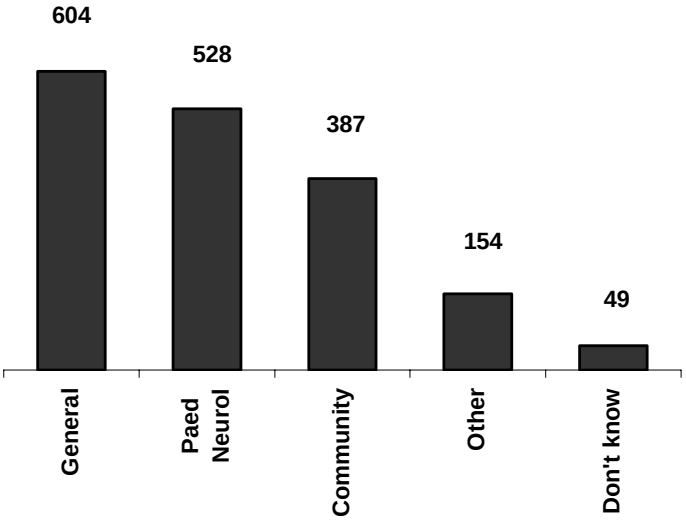


Figure 8 *Category of referring paediatrician*



Interim conclusions

PIND surveillance has now been in operation for seven years. Six cases of vCJD in children under 16 years of age at first presentation have been reported to the study. There were four cases of definite vCJD and two cases of probable vCJD. This includes the youngest ever reported case of vCJD. There have been no other PIND cases with the clinical features of vCJD, but there is concern that more childhood cases may appear. Seven years is a relatively short time to perform surveillance for a disease about which there are a number of unanswered questions. There is still uncertainty about the number of children who may be incubating vCJD, the length of the incubation period, the exact nature of transmission and the possible transmission of vCJD by blood products.

Acknowledgements

PIND surveillance is working very well and is yielding valuable information about the conditions that lead to PIND in children. Paediatricians are still responding enthusiastically with a median number of 19 notifications per month.). The PIND surveillance team is very grateful to the members of the expert neurological advisory group (Prof J. Aicardi, Dr P. Baxter, Dr S. Green, Professor R. Robinson, Professor R. Surtees and Dr J. Wilson) for all their work in classifying cases and for the cooperation of UK paediatricians in support of this surveillance project.

Ethics Approval

The Cambridge LREC has approved this study.

Funding

The Department of Health.

Support Groups

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2. Batten Disease Family Association, c/o Heather House, Heather Drive, Tadley, Hampshire, RG26 4QR
3. The Society for Mucopolysaccharide Diseases, 46 Woodside Road, Amersham, HP6 6AJ.
4. Climb, (formerly the Research Trust for Metabolic Diseases in Children (RTMDC.), The Quadrangle, Crewe Hall, Weston Road, Crewe, CW2 6UR.
5. Adrenalleukodystrophy (ALD), ALD Family Support Trust, 30-32 Morley House, 320 Regent Street, London, W1R 5AB.
6. Niemann Pick Disease Group, Kingslaw House, East Brae, East Wemyss, Fife KY1 4RS, Scotland.

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Severe complications of varicella (chickenpox) in hospitalised children

Key points

- **In a 13-month period, 156 reports have been received, of which 107 (69%) have currently been confirmed as meeting the case definition.**
- **There have been five deaths.**

Background

Varicella zoster virus causes varicella (chickenpox) on primary infection and herpes zoster upon subsequent reactivation[1]. Approximately 90% of varicella cases occur in children aged less than 15 years, with the highest incidence of infection in the one to four year age group[2,3]. Varicella is generally a mild disease, but immunocompromised individuals and neonates with maternal rash onset temporally close to birth are at greatly increased risk of complications. Nevertheless, severe complications can occur even in previously healthy children, including secondary bacterial infections, central nervous system manifestations and death[4]. There are few data on complicated varicella case in the UK. Routine hospital discharge records have been analysed previously[3,5,6], but cannot provide data with sufficient detail or accuracy.

A live-attenuated vaccine against varicella was developed in Japan in the early 1970s and has been shown to be safe and effective. It is now recommended for routine use in all healthy children in several countries, including the United States and Canada[7]. The vaccine has been reported to prevent varicella in 85% of immunised children, with 97% protection against moderately severe and severe disease[8]. There is currently no routine childhood immunisation programme against varicella in the UK or Ireland, although varicella vaccine is licensed and is currently recommended for certain seronegative healthcare workers, in addition to being available for individuals considered to be at particularly high risk of complications and their seronegative contacts. Decisions around the possible introduction of varicella vaccine are complex, and it seems doubtful whether the UK Joint Committee on Vaccination and Immunisation will recommend its administration to all healthy children in the near future. Nevertheless, data on severe complications of varicella will make a valuable contribution to the epidemiological and economic data available and will help determine the advisability of a universal or selective immunisation. If a vaccination programme were to be established, the data would also provide a baseline against which its impact could be evaluated.

Objectives

Primary

- To estimate to annual incidence of complicated varicella in hospitalised children less than 16 years of age.

Secondary

- To describe the characteristics of these complications and the affected children (e.g. age, underlying medical conditions).
- To estimate the annual financial cost of hospitalisation for severe varicella.
- To estimate the annual mortality from varicella in children.

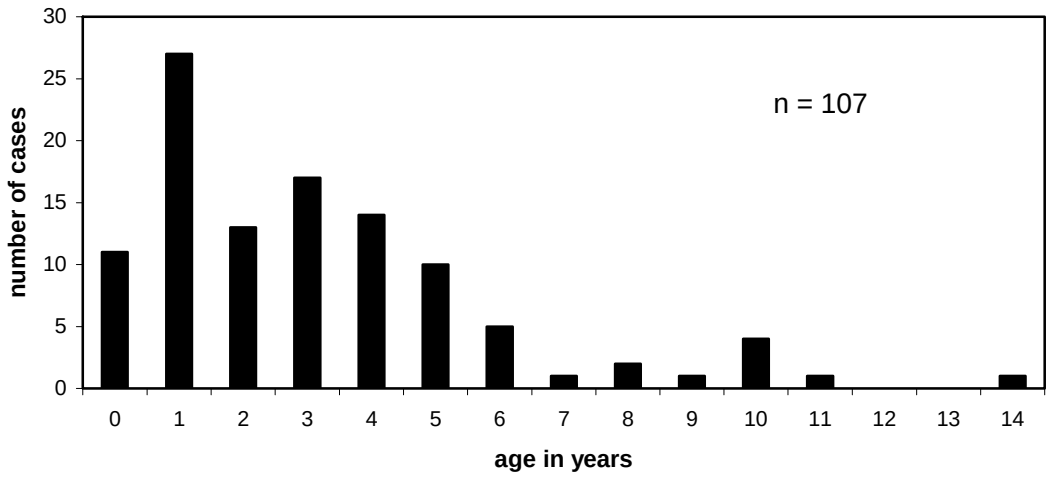
Surveillance Period

November 2002 – November 2003 (inclusive).

Case Definition

Any child aged less than 16 years hospitalised with complicated varicella, as defined by a list of clinical conditions*, or admitted to a paediatric ICU or HDU with varicella or one of its complications.

Figure 9 *Preliminary confirmed cases, by age*



*Bacteraemia/septic shock; toxic shock syndrome/toxin-mediated disease; necrotising fasciitis; encephalitis; purpura fulminans/disseminated coagulopathy; pneumonia (abnormal x-ray); fulminant varicella; Reye's syndrome; ataxia; admitted into ICU/HDU; death due to varicella.

Preliminary observations

In the 13-month surveillance period, 156 reports were received, of which 107 (69%) have currently been confirmed as non-duplicates meeting the clinical case definition within the defined period. Incidence, as determined by date of admission, peaked in March, correlating with known seasonal distribution for varicella from other sources. The ages of the confirmed cases ranged from birth to 14 years, with a median of age three years and a mode of one year (Figure 9).

The frequency of case definition criteria cited for confirmed cases is shown in Table 15. Five deaths were reported where varicella, or its complications were considered to be causative (ages: neonate, 1 year, 3 years, 10 years, 14 years).

We wish to thank everyone who has notified cases and completed questionnaires. The data continue to be analysed and will be submitted for peer-reviewed publication.

Table 15 *Frequency of case definition criteria, as cited for 107 preliminary confirmed cases*

Clinical description	Frequency
Pneumonia (abnormal x-ray)	29
Bacteraemia	27
Admitted into ICU/HDU	27
Encephalitis	25
Ataxia	17
Septic shock, Toxic shock syndrome/Toxin-mediated disease	10
Necrotising fasciitis	6
Purpura fulminans / disseminated coagulopathy	5
Fulminant varicella	5
Death	5
Neonatal varicella	3
Reye's syndrome	0
Total (n=107 cases)	**159**

Ethics Approval

Ethics approval has been received from the Scotland MREC.

Funding

Scottish Centre for Infection and Environmental Health.

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Severe hyperbilirubinaemia in the newborn

Key Points

- **In the first nine months of surveillance 61 reports had been received of which 31 have been confirmed to date. Two infants have 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 neonatal jaundice.**

Background

During the past decade, encephalopathy due to severe hyperbilirubinaemia in the newborn has been reported with increasing frequency in the United States and Europe[1, 2]. This potentially preventable condition causes substantial mortality, and neurodevelopmental morbidity in survivors. Previously it had been encountered mainly in babies with severe Rhesus isoimmunisation[3, 4], and had declined in frequency thanks to effective prevention and treatment of this condition. The reappearance of bilirubin encephalopathy has been ascribed to earlier discharge of newborn babies, and to a more relaxed approach to the management of jaundice in well term babies, particularly those breast fed[5]. These trends have occurred in Britain[6], but there have been no systematic studies reporting an increased incidence of severe hyperbilirubinaemia, nor of bilirubin encephalopathy, in Britain. The primary objective of this study is to determine the incidence of severe hyperbilirubinaemia in the newborn in the United Kingdom and Ireland.

Objectives

The aim of the study is to

- document the incidence of severe neonatal jaundice in the UK and Ireland.
- identify clinical and demographic variables associated with severe neonatal jaundice.
- document short and medium term outcomes of severe neonatal jaundice, in particular bilirubin encephalopathy and its sequelae.

Surveillance Period

June 2003 to June 2005 (inclusive).

Case Definition

Peak unconjugated serum bilirubin > 510 micromol/L in the first month of life.

Method

Paediatricians reporting cases are sent a questionnaire seeking information about the neonatal course. After 12 months, they receive a further brief questionnaire seeking information about developmental progress and outcome.

Preliminary Analysis

For the 10 months to March 2004 61 reports have been received, with 31 confirmed cases, 24 erroneous or duplicate reports, and six with no information yet available.

Confirmed cases

There were 21 male and 10 female infants. The median (range) birth weight was 3.22 kg (1.79-3.72), and median (range) gestation was 38 (35-42) weeks.

Ethnic origin: Using ONS ethnicity criteria 16 infants were classified as white, five as Asian, three as black, three mixed and four as other.

Mode of delivery: 18 infants were delivered normally, seven by caesarean section and six with the use of instruments.

Mode of feeding: 22 infants were breastfed, six had formulae milk only and three had a combination of both.

Initial discharge less than 48 hours of age: 12 infants

Median (range) peak unconjugated SBR: 590 (510-802) micromol/L

Median (range) age at peak SBR: 4 (2-10) days

Table 16 *Associated diagnoses/illnesses in reported cases*

Associated diagnosis/illness	Infants
Possible ABO incompatibility	9
Probable ABO incompatibility	2
Rhesus incompatibility	1
Hereditary spherocytosis	2
Glucose-6-phosphate dehydrogenase deficiency	2
Other haemolysis	2
Sepsis	2
Adrenal haemorrhage	1
None	10
Total	**31**

Treatment: Twenty-five infants were readmitted from home for investigation and management of severe jaundice. Twenty infants received a total of 22 exchange transfusions.

Short-term outcome: Five infants showed clinical features of bilirubin encephalopathy. One had sepsis, one had sepsis and ABO incompatibility, and the other three had haemolytic diseases. The two infants with sepsis died. Another infant was dead on admission to hospital, and so was not included under the case definition since there were no recorded serum bilirubin measurements. The infant was deeply jaundiced, however, and post-mortem showed evidence of haemolysis and kernicterus.

Comments

The data are not sufficiently complete yet to permit accurate calculation of the incidence of severe neonatal jaundice in Britain and Ireland, but both severe jaundice and bilirubin encephalopathy are occurring in near term infants. For two infants who died, co-morbidity (sepsis) may have been partly responsible.

Many affected infants were discharged early in the neonatal period, non-white infants may be disproportionately represented, most had been breast-fed and most had associated problems (notably haemolysis and sepsis), which probably aggravated their jaundice (Table 16).

With about three confirmed cases per month being reported, any missed reports will substantially affect the accuracy of calculation of the incidence of severe jaundice. We are very grateful to all paediatricians who have reported cases and completed questionnaires.

Ethics Approval

The London MREC has approved the study.

Funding

Wirral Hospital NHS Trust and the Wirral Hospital Neonatal Endowment Fund are funding the study jointly.

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Suspected fatal adverse drug reactions in children

Key Points

- **This prospective study intended to document whether fatal adverse drug reactions (ADRs) are a problem in children in the UK.**
- **Seven reports met with the case definition, however causality was not confirmed in five of these. In the remaining two cases a casual link was felt only to be a possibility.**
- **This study provides no evidence to suggest that there is a major public health problem relating to fatal ADRs in children.**

Background

The Yellow Card Scheme, set up in 1964 and administered by the Medicines and Healthcare products Regulatory Agency (MHRA), is the UK's spontaneous reporting scheme and is the mainstay of drug safety monitoring in the UK. It is possible that there may be under-reporting of suspected adverse drug reactions (ADRs) in children. Medicines in children are frequently prescribed "off-label" and therefore have not been formally evaluated for safety and efficacy in that age group. It is particularly important to report and detect potential drug safety issues in children. It was hoped that this prospective study would for the first time allow us to document whether fatal adverse drug reactions are a significant problem in children.

Objective

To study the frequency and nature of suspected adverse drug reactions with a fatal outcome in children below the age of 16 years.

Surveillance Period

June 2002 – June 2003 inclusive.

Methodology

All cases meeting the case definition were identified using the BPSU Orange Card. The MHRA Yellow Card scheme remained in operation as a parallel reporting system and it was expected that health professionals would report each case through this system also. Details of each case were sought through a written questionnaire sent to the reporting clinician. If necessary, a further follow-up letter was sent. The patient or family were not contacted. An expert panel consisting of five members (with expertise in paediatrics, neonatology, paediatric pharmacy, paediatric pathology and pharmacovigilance) undertook causality assessment of each case[1].

Case Definition

Clinicians were asked to report any child below the age of 16 years with a suspected adverse drug reaction with a fatal outcome. ADRs included suspected reactions to vaccines.

Analysis

During the period 1 June 2002 to 30 June 2003, 16 notifications of suspected fatal ADRs in children <16 years were received by the MHRA for this study. In two cases, the reporter subsequently denied reporting. For one case, a Yellow Card had been received in April 2002 and so this report was deemed to be outside the required timeframe. One questionnaire was not returned. There were two triplicate cases and one case reported twice by the same reporter. Seven reports meeting the study criteria remained. Of these seven cases, five were considered by the Expert Panel to be unlikely to be causally related to the suspect drug. In the remaining two cases, the suspected drugs were enalapril and sodium valproate and causality assessment was not unanimous among the panel members.

Three of these reports were also reported to the Yellow Card scheme, one to the Yellow Card scheme first, the other two after reporting via BPSU. During the same reporting period there were an additional 16 reports of ADRs with a fatal outcome in children reported through the Yellow Card scheme. These reports were of varying quality and completeness and subject to the usual limitations of spontaneous reporting.

Conclusions

The number of suspected fatal ADRs reported in this study has been low. Three consultant paediatricians reported via the Yellow Card scheme and not through this BPSU study. Possible reasons for this low response include:

- The number of ADR-related deaths in children is genuinely low.
- ADRs with a fatal outcome may be under-recognised by clinicians as these tend to occur in sick children on multiple drugs.
- There may be a reluctance to report, even in an anonymised way, deaths due to off-label or unlicensed prescribing of drugs to children.

However this study gives no evidence that there is a major public health problem relating to fatal ADRs in children.

Ethical approval

This study was approved by the London MREC.

Funding

The Medicines and Healthcare products Regulatory Agency, formerly The Medicines Control Agency, UK.

References

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Tuberculosis in childhood

Key Points

- **The primary aim of the study is to estimate the incidence of tuberculosis in children aged less than 16 years of age in the UK and Ireland.**
- **The study will allow the validation of the enhanced surveillance system currently in place.**

Background

Overall tuberculosis (TB) notification rates in the United Kingdom have levelled off in the last few years at 10-11 /100,000 population. Notification rates in London, however, have quadrupled in the last decade to approximately 40 /100, 000 population and, in some areas within London, rates now exceed 100 /100,000. Increased immigration from high prevalence countries and HIV infection has been suggested as factors leading to resurgence in some areas in the UK. Paediatric TB notifications have also increased at a rate greater than the overall TB notification rate in general with some London boroughs witnessing a 130% increase[1]. Paediatric TB cases are especially important in that they often represent sentinel events in a population reflecting recent transmission from an infectious adult, who may be at risk to others.

National data on paediatric TB are derived from statutory notifications and, since 1999, through the enhanced surveillance system. Additional information is available from Mycobnet, which is a system to monitor anti-tuberculosis drug resistance in the UK, and provides information on species, drug sensitivity results, and some demographic data. However, it is unclear how accurate and complete these methods are in determining the true incidence of childhood TB. Retrospective data have suggested both over-notification and considerable under-notification of childhood tuberculosis[2,3]. Enhanced surveillance has been in operation in England and Wales since 1999 but its completeness and accuracy in ascertaining cases of childhood TB has not been validated. In addition, there is limited information on the clinical spectrum of TB disease seen in children in the UK. Pulmonary disease remains the commonest form of childhood TB but numbers of children with central nervous system disease have been increasing in London (P. Atkinson, CDSC unpublished data) and have been reported to represent an unusually high proportion of all childhood TB cases (10% compared with rates of 1% in South Africa and 5-8% in the USA)[3].

The Chief Medical Officer (CMO) for England has published a strategy for health protection entitled *Getting Ahead of the Curve*[4]. In this strategy TB was identified as a key infectious disease problem requiring intensified control measures to reduce illness and death. An infection strategy for children has been proposed as part of the children's National Service Framework where priority will be given to preventative services and clinical care for children with infections[5,6]. A BPSU study will be important not only in estimating the incidence of TB and validating the enhanced TB surveillance system but also to inform the development of services for children with TB.

Objectives

The aim of this study is 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.

Surveillance Period

December 2003 – December 2004 (inclusive).

Case Definition

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 antituberculous drugs

We would like to remind you that all cases should also be reported to the Enhanced Surveillance Program.

Analysis

BPSU surveillance has been in operation for five months. Up to April 2004 there were 126 notifications and 91 completed questionnaires have been returned. There were 63 confirmed cases of childhood TB (Table 17). Fifty-seven cases were from England (90 %) with 20 of these in London (32%). Five were from Wales (8%) and one from Scotland (2 %).

As the study continues and further cases are collected it will be possible to present more detailed analysis.

Table 17 *Cases of childhood tuberculosis to April 2004 by age and sex*

Age (years)		≤ 3	4 – 7	8 – 11	12 - 15	**Total**
No of cases	Male	6	10	7	6	**29**
	Female	11	6	5	12	**34**
Total		**17**	**16**	**12**	**18**	**63**

Ethics Approval

This study has been approved by the South West MREC.

Funding

Department of Child Health, Royal London Hospital.

Support Group

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6 New Studies 2004

Neonatal herpes simplex virus (HSV) infection

Background

Neonatal herpes simplex virus (HSV) infection is a rare but potentially devastating condition. It can follow primary or recurrent maternal infection, or be acquired postnatally through direct contact with infected secretions. Transplacental transmission is unusual, and perinatal infection is usually acquired during vaginal delivery through an infected birth canal.

The relative contribution of primary and recurrent maternal infection to neonatal disease, the prevalence of neonatal infection and the proportion of neonatal disease associated with HSV-1 and HSV-2 varies between countries. Primary maternal infection close to term is estimated to lead to neonatal infection in about one third of cases, and to be about 10 times more likely than a recurrence of maternal infection to result in neonatal infection. Prior infection with HSV-1 is partially protective against the acquisition of HSV-2. Although oral infection is predominantly associated with HSV-1, and genital infection with HSV-2, there is considerable crossover, and genital HSV-1 is common, and becoming more so. However, the majority of women who have had genital HSV are probably not aware of the fact. Both primary infection and reactivation can be asymptomatic.

Neonatal presentation and outcome

Infants who present with disease *localised* to the skin, eye and/or mouth (SEM) have the best prognosis and death is unusual, although impairment can occur, possibly associated with sub-clinical CNS infection. Those who present with acute *disseminated* HSV infection have multiple organ involvement, including the liver, lungs, gastrointestinal tract and CNS; the likelihood of death is high, and nearly all survivors have severe handicap. Infants with *encephalitis confined* to the CNS often present late, and may not develop skin lesions; the mortality rate is around 50%, and the long-term prognosis is poor for those who survive.

Early diagnosis is vital in all cases since antiviral therapy can significantly affect outcome.

Surveillance of neonatal HSV was previously undertaken through the BPSU in 1986-1991. The estimated prevalence of infection was then 1.65/100,000 (CI 1.3-2.0/100,00). HSV-1 and HSV-2 were reported in equal proportions, but in one third of cases the virus was not typed. Approximately equal numbers of infants presented with localised, disseminated and CNS infection. Given the rarity of the condition, and the observation that most infants were born to women with no prior history of infection, it was considered at that time that antenatal screening was not justified.

There have been important changes in the demographic profile of the British population in the last 15 years, and there is increasing concern about the prevalence of sexually transmitted diseases; these factors could also have contributed to an increase in the incidence of neonatal HSV in the British Isles.

Objectives

The aim of this study is to

- estimate the current birth incidence of neonatal herpes infection (HSV-1 and HSV-2) in the British Isles.
- explore the presentation of neonatal infection, and management of diagnosed cases.
- assess morbidity and mortality at one year follow up through the notifying paediatrician.
- compare findings with the 1986-91 BPSU cohort, and with INoPSU studies currently being undertaken in Australia and Canada.

Surveillance Period

February 2004 – February 2005 (inclusive).

Surveillance case definition

1. Any infant under one month -
   (a) with a diagnosis of HSV infection, based on virus culture, or serology, or PCR, or
   (b) treated with antiviral drugs for suspected HSV infection
2. Any stillborn infant in whom HSV infection is suspected.

Analytic case definition

Confirmed case of neonatal HSV:

1. Virus culture, specific IgM, PCR confirming HSV infection on a specimen taken in the first four weeks of life, or
2. Typical clinical manifestations with maternal infection confirmed by either seroconversion or virus isolation around the time of delivery

Suspected case of neonatal HSV:

1. Typical clinical manifestations and treated with antiviral drugs for suspected HSV infection.

Funding

Departmental Funds.

Ethic Approval

This study has been approved by the London MREC.

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Medium Chain Acyl CoA Dehydrogenase Deficiency

Background

Medium chain acyl CoA dehydrogenase deficiency (MCADD) is a recessively inherited metabolic disorder, which has been identified as a strong candidate for newborn screening through two systematic reviews commissioned by the Health Technology Assessment Programme . The authors of these reviews concluded that more UK based data were required to inform screening policies based on tandem mass spectrometry. Subsequently, the Department of Health and National Screening Committee have funded a pilot newborn screening service for MCADD, which started in March 2004 in certain areas of England. They have also commissioned a concurrent research study to evaluate this pilot service.

Although the findings of a number of primary studies of MCADD screening in other countries have been reported, important questions relevant to screening policy remain unanswered, including clinical outcome following detection through newborn screening and screening programme performance in a UK setting. Furthermore, the generalisability of findings from these studies is uncertain, as screening is carried out several days later in the UK. It is therefore vital to ensure that performance and longer-term clinical outcomes of screening are carefully evaluated in a UK setting.

The research study will obtain estimates of the false negative rates of screening for MCADD. Importantly it will 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 these endeavours. Screening is being carried out over two years in six laboratories covering at least half of all UK births each year. All screen positive infants are being followed to ascertain final diagnosis and outcome to two years following detection. This information will be used to estimate the prevalence and genotype distribution of MCADD ascertained through screening. Concurrently, clinically diagnosed cases of MCADD will be identified and followed through the BPSU so that detection rates can be estimated and clinical outcomes compared amongst screened and unscreened populations. The primary clinical outcome for the study is encephalopathy-free survival to two years of age. This outcome reflects the fact that median age at death in clinical case series is 14 months, that most acute events will have occurred by two years of age and that the majority of clinical diagnoses will have been made by this age.

The British Inherited Metabolic Disease Group (BIMDG), the parent support group - Children Living with Inherited Metabolic Disease (CLIMB) - and the UK Newborn Screening Laboratory Network (UKNSLN), supports this study.

Objective:

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 2005 (inclusive).

Case Definition

MCADD is one of the most common of the fatty acid oxidation defects. These are disorders of intermediary metabolism that may cause hypoglycaemia, acute encephalopathy and sudden death. During an intercurrent illness, particularly gastroenteritis, there may be progressive encephalopathy with drowsiness, hypoglycaemia, lethargy and hypotonia progressing to coma. Children with MCADD usually present clinically before the age

of two. 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.

MCADD is recessively inherited and between 1 in 40 and 1 in 80 of the UK population are unaffected carriers. Approximately 80-90% of affected individuals have the same genetic mutation (G985A), with the majority of the remainder being heterozygous for this mutation. From this it is predicted that the birth prevalence is about 1 in 10,000 (1 in 6,500 to 1 in 20,000).

The diagnosis of MCADD can be made following clinical presentation, diagnosis in an affected family member or through newborn screening. A child will be considered to have a diagnosis of MCADD if the following criteria are met:

- Elevated octanoyl carnitine in the presence of normal free carnitine levels on blood test using tandem mass spectrometry

AND/OR

- Characteristic urine profile of organic acids with hexanoyl, suberyl and phenylpropionyl glycine

WITH OR WITHOUT one or both of the following:

- 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 MCADD

Methods

Paediatricians are asked to notify cases on the orange card through the BPSU in the usual way. These notifications will be forwarded to study investigators at the Institute of Child Health who will send a case notification questionnaire to the notifying paediatrician. This will be followed approximately four months later by a brief questionnaire to confirm diagnosis. Follow-up questionnaires will be sent to establish clinical outcome at one and two years following diagnosis.

No specimens will be required.

All the requirements of the Data Protection Act and Caldicott arrangements will be followed.

Ethics Approval

This study has been approved by the London GOS MREC (no local investigator status).

Funding

Department of Health.

Support Group

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Tel: 0800 652 3181. Web: http://www.climb.org.uk/Climb

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Thyrotoxicosis in Childhood

Background

The incidence of thyrotoxicosis in children in the UK and 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/year (Iceland, 10-19 yr olds)[2]. The incidence in Hong Kong was recently reported as 6.5/100,000/year[3]. The mean age of diagnosis there has been reported as 11.34 years with a female:male ratio of 5.5:1[4].

Based on the above incidences, a conservative estimate for the UK childhood population (11.7 million on 2001 census) would be over 90 new cases per year.

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 TSH, but diagnosing the underlying condition may be more difficult. Clinicians may rely on history, clinical findings and basic thyroid function tests (TSH and Free T4 assay) 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].

Serious complications of the antithyroid drugs have been reported, particularly agranulocytosis and most often in the first three months of therapy but it is not clear how frequently these occur in children and how this affects subsequent treatment [8,9].

This study aims to be a comprehensive survey of childhood thyrotoxicosis in the UK and Ireland in order to make the best data available on the current incidence, patterns of presentation and management of this disease. As well as an increased understanding of this disease, the provision of this data is expected to direct future studies, and give clues to the best management of children with this condition.

Objectives

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

Surveillance Period

Autumn 2004 – Autumn 2005.

Analytic case definition

1. Thyrotoxicosis: A child below the age of 16 with a syndrome of signs and symptoms caused by high levels of circulating thyroid hormones and confirmed with laboratory finding of high serum levels of T4 and or T3.
2. Graves' Disease: A child with signs and symptoms of thyrotoxicosis and a diffuse goitre confirmed by laboratory analysis with undetectable levels of plasma TSH (< 0.1 mU/l) and high levels of T4 and/or T3 (outwith the local reference range). May or may not be further confirmed by presence of high levels of circulating thyroid stimulating immunoglobulins, absence of nodules on ultrasound scan of thyroid, and diffuse increased uptake of radioisotope into thyroid.

Surveillance case definition

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

Ethics approval

The Scottish MREC is in the process of reviewing this study.

Funding

RCPCH Sir Peter Tizard Bursary.

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Obesity-related type 2 diabetes

Background

Type 2 diabetes related to obesity is a newly emerging problem in children in the developed world. Although it has been known for sometime that there is an increased risk of Type 2 diabetes in specific ethnic populations with a genetic susceptibility, the first cases in obese white adolescents have recently been reported in the UK[1] and the group reporting this finding have now identified 11 cases from their single large diabetes clinic. These findings together with those from a national survey of UK paediatric endocrinologists in 2000 which identified 24 cases of type 2[2], suggest that the changing incidence seen in the USA in the 1990's, where type 2 as a proportion of in all new cases of diabetes in children increased from 2-4% in 1992 to 8-45% in 1999[3], is beginning to happen in the UK a decade later.

Type 2 diabetes presentation, diagnosis and outcome

Because type 2 diabetes in children is still rare, relatively little is known about the clinical features of presentation, how it is diagnosed, what are the optimal treatment and management strategies and what, if any, is the short-term morbidity. Furthermore Type 2 diabetes in children can be a challenge for clinicians to diagnose. Although there are certain clinical features highly suggestive of Type 2 (non immune-mediated) diabetes such as obesity, a family history of Type 2 diabetes, acanthosis nigricans and polycystic ovary syndrome, it can have clinical presentations indistinguishable from those with Type 1 (e.g. DKA). As a result many clinicians classify the type of diabetes on clinical features and course of the illness without ordering confirmatory antibody tests for Glutamic acid decarboxylase (GDA) and Islet cell autoantibodies (ICA). This approach is likely to lead in some cases to either misdiagnosis, delays in diagnosis or inappropriate treatment.

There is therefore a clear need for studies of obesity-related type 2 diabetes in children to establish the current UK incidence as a benchmark for future studies on changing incidence and to investigate how paediatricians are diagnosing and managing the condition.

Objectives

The aim of the study is to:

- Establish the UK and Ireland incidence of all non-type 1 diabetes in children 0-16 years
- Determine the relative incidence of obesity-related type 2 diabetes and other syndromic diabetes.
- Characterise the clinical features at presentation for the different types of non-type 1 diabetes, which will inform paediatricians about which clinical features distinguish type 2 from other cases of non-type 1 diabetes.
- Identify how type 2 diabetes is being diagnosed and treated by paediatricians.
- Identify any short-term morbidity associated with obesity-related diabetes.

Surveillance Period

Autumn 2004 – Autumn 2005.

Surveillance case 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). NB 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).

Analytic case definition

Any case of confirmed obesity–related Type 2 diabetes.

Ethical approval

The South West MREC are in the process of reviewing this study.

Funding

Diabetes UK.

Support Group

Diabetes UK Careline, 10 Parkway, London Nw1 7AA. Helpline tel: 0845 120 2960

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7 International Network of Paediatric Surveillance Units

Background

Following the success of the BPSU, the same methodology was adopted and adapted in the 1990s by 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 more common 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.

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. Units now contact each other for results, share protocols, and put researchers in touch with each other. A common international report is shared as part of national reports.

The Network was formed in August 1998 at a meeting of the 10 units expressing 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.

Details on the activities of each surveillance unit is available from their respective websites and also from the INoPSU website.

Report of the 3rd INoPSU Conference

Following similar meetings in Ottawa in 2002 and York in 2002, the Portuguese Paediatric Surveillance Unit hosted the third INoPSU conference. This conference was held over three days during April in Lisbon.

The morning of day one saw presentations from various disease surveillance registries, including the Portuguese birth defect registry, the registry for primary immunodeficiencies and the Spanish epidemiological network on rare disease research. Presentations from Orphanet (www.orpha.net) a web based database of rare disease and orphan drugs and the newly established network of public health institutions on rare disease (NEPHRID) were received. The afternoon session concentrated on discussions in areas of concern to the surveillance units. Firstly there was a discussion on how to appropriately recognise the work the reporting physicians make to the surveillance system and how they should be acknowledge in papers. Following this discussion it was agreed that INoPSU should prepare an addendum to the Vancouver protocol on authorship of scientific papers, aimed at national studies of rare disease. The second discussion of the afternoon centred on the completeness of ascertainment of case reports. The use and fallibilities of capture-recapture techniques were reviewed. The BPSU through their medical advisers also presented their analysis of the effectiveness of using different sources for case ascertainment e.g. adult specialty groups, laboratory data and patient support organisations.

Day two saw papers presented on conversion disorder in Australian children, invasive fungal infection in very low birth weight children in the UK, group b streptococcal infection in Portugal. Of particular interest was the six country international collaborative paper on surveillance of haemolytic uraemic syndrome, comparing and contrasting the disorder across nations. A very important paper for all surveillance units was that outlining the extensive evaluation of the Canadian paediatric surveillance program. This evaluation, based on the Centers for Disease Control and Prevention (CDC) guidelines on evaluating surveillance systems, measured the effectiveness of the Canadian surveillance program which we were pleased to hear scored very highly.

The final day brought together 21 representatives from 11 of the 14 national surveillance units (Table 18) and the British Ophthalmology Surveillance Unit for the business meeting. Professor Mike Preece, the BPSU Scientific Co-ordinator, Richard Lynn represented the UK. Countries represented at the meeting included the hosts Portugal, Germany, Netherlands, Australia, New Zealand, Ireland, Switzerland and Canada. The aims of INoPSU were defined as the facilitation of communication between existing units; encouragement of the sharing of information between researchers and assistance in the development of new units. With the final aim in mind, the Greece/Cyprus surveillance unit was accepted as a full member of INoPSU whilst the Trinidad and Tobago Unit was accepted as an affiliate until such time as it has fulfilled the requirements

for entry. The meeting also heard that both Argentina and Poland were interested in setting up similar units.

Topics discussed included the future funding of INoPSU to fulfil its aims, the difficulties surrounding consent, confidentiality data collection and handling and the need for multi-national rare disease surveillance. Ways in which communications can be improved by national research teams were also proposed and it is hoped that this will stimulate the use of multi-national surveillance protocols.

The meeting was considered a great success and should hopefully be repeated in 2006. Copies of the abstracts are available via the BPSU office or online at http://bpsu.inopsu.com/Whatsnew.htm. Further information on INoPSU is available online at http://www.inopsu.com.

Table 18 *INoPSU Units*

Country	Child population (10^6 aged 0-15 yrs)	Established	Respondents	Reply paid	Response Rate	Fee for study
Australia	3.9	1992	1042	Yes	96%[1]	Yes
UK/Ireland	12.8	1986	2324	No	93%	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	129[5]	No	94%[5]	No
Ireland	1.0	1996	135	Yes	85%	Yes
Portugal	1.8	2001	1500	Yes	30%	Yes
Greece/Cyprus	1.6	2001	310	No	93%	Yes

[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.
[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 1986-2003

By mid-2003 the BPSU had completed 55 studies. Information about these studies has been included in previous annual reports of the BPSU, which are available from the BPSU office. The studies, principal investigators and definitive papers are listed below.

X-linked anhydrotic ectodermal dysplasia
Surveillance Period: June 1986 - August 1986
Investigator: Dr A Clarke
Published paper: X-linked anhydrotic ectodermal dysplasia. Clarke D. BPSU 2nd Annual Report 1987. BPSU London

Haemorrhagic shock encephalopathy syndrome
Surveillance Period: June 1986 - December 1988
Investigator: Dr S Hall
Published Paper: Haemorrhagic Shock Encephalopathy Syndrome in the British Isles. Bacon CJ, Hall SM. *Arch. Dis. Child.* 1992; **67**: 985-993

Haemolytic uraemic syndrome I
Surveillance Period: June 1986 - December 1989
Investigators: Dr C M Taylor, Dr D Milford, Dr S Hall
Published paper: Haemolytic Uraemic Syndrome in the British Isles 1985-88; Association with Verocytotoxin-Producing *E.coli*: Milford DV, Taylor CM, Guttridge B, Hall SM, Rowe B, Kleanthous H. *Arch. Dis. Child.* 1990; **65**: 716-72

Kawasaki disease
Surveillance Period: June 1986 - December 1992
Investigator: Dr S Hall
Published Paper: Kawasaki Disease in the British Isles. A survey of management: Dhillon R, Newton L, Rudd PT, Hall SM *Arch. Dis. Child.*1993. **69**: 631-638
Kawasaki disease - Lessons for Britain: Bissenden JG, Hall SM. *BMJ.* 1990; **300**: 1025-1026

Lowe syndrome
Surveillance Period: June 1986 - February 1988
Investigator: Dr C McKeown
Published Paper: Lowe Syndrome. McKeown C. BPSU 2nd Annual Report. 1987. BPSU London

Neonatal herpes
Surveillance Period: June 1986 - December 1991
Investigators: Dr PA Tookey, Professor C S Peckham, Dr R Dinwiddie
Published Paper: Neonatal herpes simplex virus infection in the British Isles: Tookey P, Peckham CS.
Paediatr. Perinat. Epidemiol. 1997; **10**: 432-442

Insulin dependent diabetes in under fifteens
Surveillance Period: January 1988 - December 1988
Investigator: Professor J D Baum
Published paper: Incidence of Insulin Dependent Diabetes in Children Aged Under 15 Years in the British Isles During 1988: Metcalfe MA, Baum JD. *BM J* 1991; **302**: 443-7

Drowning and near drowning
Surveillance Period: January 1988 - December 1989
Investigators: Professor J Sibert, Dr A Kemp
Published Paper: Drowning and near drowning in children in the United Kingdom: lessons for prevention: Kemp A, Sibert JR. *BMJ.* 1992; **306**: 291-297
Outcome in Children Who Nearly Drown: a British Isles Study: Kemp AM, Sibert JR. *BMJ* 1991; **302**: 931-933

Haemorrhagic disease of the newborn
Surveillance Period: March 1988 - February 1990
Investigators: Dr AW McNinch, Dr H Tripp
Published paper: Haemorrhagic Disease of the Newborn in the British Isles: a two year prospective study: McNinch AW, Tripp JH. *BMJ* 1991; **303**: 1105-1109

Galactosaemia
Surveillance Period: January 1988 - September 1991
Investigators: Mrs A Green, Dr J Holton, Dr M Honeyman, Professor J Leonard
Published paper: Galactosaemia, Results of the British Paediatric Surveillance Study 1988-90: Honeyman MM, Green A, Holton JB, Leonard JV. *Arch. Dis. Child.* 1993; **69**: 339-341

Congenital toxoplasmosis
Surveillance Period: June 1989 - May 1990
Investigator: Dr S Hall
Published paper: Screening for Toxoplasmosis during Pregnancy: Peckham CS, Logan S. *Arch. Dis. Child.* 1993; **68**: 3-5

Higher order births
Surveillance Period: January 1989 - December 1989
Investigator: Professor M Levene
Published paper: Higher multiple births and the modern management of infertility in Britain. For the British Association of Perinatal Medicine: Levene MI, Wild J, Steer P.
Br. J. Obst. Gynaecol. 1992; **99**: 607-613

Acute rheumatic fever
Surveillance Period: January 1990 - December 1990
Investigators: Dr C Boyd-Scobie, Dr S Hall
Published paper: BPSU 5th Annual Report. BPSU London 1990

Rett syndrome

Surveillance Period: April 1990 - June 1990
Investigator: Dr A Kerr
Published paper: Rett Syndrome: British Longitudinal Study (1982-1990) and 1990 Survey. In Mental Retardation and Medical Care. Roosendaal JJ (ed.). Uitgeverij Kerckebosch, Zeist 1991

Measles, mumps, rubella-meningococcal meningitis

Surveillance Period: Jan 1990 - December 1991
Investigator: Dr N Begg
Published paper: Meningoencephalitis associated with MMR vaccine: Maguire HC, Begg NT, Handford SC. *Communicable Disease Report* 1991; 1 (**6**): R57-R59

Chemistry set poisoning

Surveillance Period: January 1991 - April 1992
Investigator: Dr E Mucklow
Published paper: Chemistry Set Poisoning: Mucklow ES. *Internat. Journ. Clin. Pract.* 1997; **51.5**: 321-23

Acute flaccid paralysis

Surveillance Period: July 1991- June 1994
Investigator: Dr N Begg
Published paper: Polio Eradication: Surveillance Implications for the United Kingdom: Salisbury DM, Ramsay ME, White JM, Brown DW. *Infect. Dis*. 1997; **175 (Suppl 1)**: S156-9

Androgen insensitivity syndrome

Surveillance Period: September 1991 - August 1993
Investigator: Professor IA Hughes
Published paper: Androgen Insensitivity syndrome: a survey of diagnostic procedures and management in the UK. Viner RM, Teoh Y, Williams DM, Patterson MN, Hughes IA. *Arch. Dis. Child.* 1997; **77**: 305-309

Long term parenteral nutrition

Surveillance Period: February 1992 - April 1992
Investigators: Professor D Candy, Professor E Ross,
Dr S P Devane
Published paper: Survey of children on long term parenteral nutrition, UK and Eire 1992. Devane S P. Abstract RCPCH Scientific Meeting 1993

Insulin dependent diabetes in under fives

Surveillance Period: January 1992 - December 1992
Investigators: Professor JD Baum, Ms E Wadsworth
Published Paper: Insulin dependent diabetes in children under five: incidence and ascertainment validation for 1992.
BMJ 1995; **67**: 700-703
Dermatoglyphics, fetal growth and insulin dependent diabetes in children under five: Shield JP, Wadsworth EJ, Hobbs K, Baum JD. *Arch. Dis. Child*. 1995 **72(2)**: 159-60

Juvenile dermatomyositis

Surveillance Period: June 1992 - December 1993
Investigators:Dr D Symmons, Dr A Sills
Published Paper: The incidence of juvenile dermatomyositis: results from a nationwide study: Symmons DP, Sills JA, Davis SM. *Br. J. Rheumatol.* 1995; **34**: 732-736

Congenital dislocation of the hip

Surveillance Period: April 1993 - July 1993
Investigators: Dr C Dezateux , Dr S Godward
Published Paper: A national survey of screening for congenital dislocation of the hip: Dezateux C, Godward S. *Arch. Dis. Child*. 1996; **74**: 445-448
Screening for congenital dislocation of the hip in the newborn and young infants. Dezateux C, Godward S. Edinburgh 1997; Churchill Livingstone

Haemophagocytic lymphohistiocytosis

Surveillance Period: September 1991 - August 1994
Investigators; Professor S Strobel, Dr M Taylor, Dr J Pritchard
Published Paper: 10th BPSU Annual Report 1995/96. BPSU London 1995

Non-accidental poisoning/ Munchausen syndrome by proxy

Surveillance Period: September 1992- August 1994
Investigator: Dr P Davis, Professor J Sibert, Professor SR Meadow, Dr R McClure
Published paper: The epidemiology of Munchausen Syndrome by Proxy, Non-accidental poisoning and Non-accidental suffocation: McClure RJ, Davis PM, Meadow SR, Sibert JR. *Arch. Dis. Child.* 1996; **75**: 57-61

Neonatal necrotising enterocolitis

Surveillance Period: October 1993 - October 1994
Investigators: Professor A Lucas, Ms R Abbott
Published Paper: Neonatal necrotising enterocolitis: 11th BPSU Annual Report 1996/7. London 1997

Vitamin K deficiency bleeding II

Surveillance Period: January 1993 - December 1994
Investigators: Dr A McNinch, Dr J Tripp
Vitamin K Deficiency Bleeding: McNinch A, Tripp J
Published paper: 9th BPSU Annual Report 1993/94. BPSU London 1994

Biliary Atresia

Surveillance Period: March 1993 - February 1995
Investigators: Dr JP McKiernan, Dr D Kelly, Dr AJ Baker
Published paper: The frequency and outcome of biliary atresia in the UK and Ireland McKiernan JP, Baker AJ, Kelly D.
Lancet 2000; **355**: 25 - 29

Transient and permanent neonatal diabetes

Surveillance Period: July 1994- August 1995
Investigator: Dr J Shield, Professor JD Baum, Ms E Wadsworth
Published paper: Aetiopathology and genetic basis of neonatal diabetes: Shield JP, Gardner RJ, Wadsworth EJ, Whiteford ML, James RS, Robinson DO, Baum JD, Temple IK.
Arch. Dis. Child. 1997; **76**: F39-F42

Adverse neonatal outcomes of delivery or labour in water

Surveillance Period: April 1994- April 1996
Investigators: Dr P Tookey, Dr R Gilbert
Published paper: Labour and birth in water in England and Wales. Aldernice F, Renfrew M, Marchant S, Ashurst H, et al. *BMJ* 1995; 310: 837
Perinatal mortality and morbidity among babies delivered in water: surveillance study and postal survey Gilbert RE and Tookey PA. *BMJ* 1999; **319**: 483-487.

Congenital syphilis

Surveillance Period: July 1993 - July 1996
Investigators: Dr A Nicoll, Dr T Lissauer
Published paper: Syphilis in pregnant women and their children in the United Kingdom: results from national clinician reporting surveys: Hurtig A-K, Nicoll A, Carne C, Lissauer T et al**.**
BMJ. 1998; **317**: 1617-9

Congenital cataract

Surveillance Period: October 1995 - October 1996
Investigator: Dr J Rahi
Published paper: National cross sectional study of detection of congenital and infantile cataract in the United Kingdom: role of childhood screening and surveillance: Rahi JS, Dezateux C.
BMJ 1999; **318**: 362-365
Capture-recapture analysis of ascertainment by active surveillance in the British Congenital Cataract Study: Rahi JS, Dezateux C, for the British Congenital Cataract Interest Group*: Invest. Ophthalmol. Vis. Sci*. 1999; **40**: 236-239

Medium chain acyl-CoA dehydrogenase

Surveillance Period: March 1994 - March 1996
Investigators: Dr R J Pollitt, Prof J Leonad
Published paper: Prospective surveillance study of medium-chain CoA dehydrogenase deficiency in the United Kingdom: Pollitt RJ, Leonard JV. *Arch. Dis. Child.* 1998; **79**: 116-119
Neonatal screening for inborn errors of metabolism: cost, yield and outcome: Pollitt R J, Green A, McCabe CJ, et al. Health Technology Assessment Report 1997

Pyroxidine dependent seizures

Surveillance Period: September 1995 - October 1996
Investigator: Dr P Baxter
Published paper: Epidemiology of pyridoxine dependent and pyridoxine responsive seizures in the UK. Baxter P.
Arch. Dis. Child. 1999; **81(5)**: 431-3.

Neonatal meningitis

Surveillance Period: July 1996 - December 1997
Investigators: Dr D Holt, Mrs S Halkett
Published Paper: Neonatal meningitis in England and Wales: 10 years on. Holt DE, Halket S, de Louvois J, Harvey D.
Arch. Dis. Child. Fetal Ed. 2001; **84**:F85-F89

Cerebral oedema and death following diabetic ketoacidosis

Surveillance Period: October 1995 - September 1998
Investigators: Dr J Edge, Dr M Hawkins
Published Paper: The risk and outcome if cerebral oedema developing during diabetic ketoacidosis. Edge JA Hawkins MA, Winter DL, Dunger DB. *Arch. Dis. Child.* 2000; **85**: 16-22

Hepatitis C virus (HCV) infection

Surveillance Period: March 1997 - March 1999
Investigators: Dr D Gibb, Ms P Neave
Published paper: Active surveillance of hepatitis C infection in the UK and Ireland. Gibb DM, Neave PE, Tookey PA, Ramsay M, Harris H, Balogun K, Goldberg D, Mieli-Vergani G, Kelly D. *Arch. Dis. Child*. 2000; **82(4)**: 286-91

Congenital brachial palsy

Surveillance Period: March 1998- March 1999
Investigators: Dr G Evans-Jones, Mr S P J Kay, Professor M Weindling
Published Paper: Congenital brachial palsy: incidence, causes, and outcome in the United Kingdom and Republic of Ireland. Evans-Jones G, Kay S P J, Weindling A M, Cranny G, Ward A, Bradshaw A, Hernon C. *Arch. Dis. Child. Fetal Neonatal Ed.* 2003; **88**: F185-F189

Subdural haematoma and effusion

Surveillance Period: April 1998- April 1999
Investigators: Dr C Hobbs, Dr J Wynne, Dr A M Childs
Published Paper: 14th BPSU Annual Report 1999/00. BPSU London 2000

Inflammatory bowel disease in under 20 year olds

Surveillance Period: June 1998-June 1999
Investigators: Professor B Sandhu, Dr A Sawczenko
Published Paper: Prospective survey of childhood inflammatory bowel disease in the British Isles Sawczenko A, Sandhu B K Logan, R F A, Jenkins H, Taylor C J, Mian S, Lynn R.
Lancet 2001; **357**: 1095-96

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: September 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
Investigatosr: Dr M Taylor, Dr D Milford, Dr B Adak, Mr R Lynn, Dr M Locking, Dr S O'Brien
Published Paper: 15th BPSU Annual Report 2000/01. BPSU London 2001

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: 15th BPSU Annual Report 2000/01.
BPSU London 2001

Encephalitis in Early Childhood (2 months – 3 years)

Surveillance Period: October 1998 – September 2001
Investigators: Dr K Ward, Professor E Ross
Published Paper: 16th BPSU Annual Report 2001/02.
BPSU London 2002

Cerbrovascular 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

Congeital 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: 17th BPSU Annual Report 2002/03.
BPSU London 2003

Appendix B Published papers 2003-4

Hib vaccination in infants born prematurely. Heath P T, Booy R, McVernon J, Bowen-Morris J, Griffiths H, Slack M P E, Moloney A C, Ramsay M E, Moxon E R
Arch. Dis. Child. 2003; **88**: 206-210.

Congenital brachial palsy: incidence, causes, and outcome in the United Kingdom and Republic of Ireland. Evans-Jones G, Kay S P J, Weindling A M, Cranny G, Ward A, Bradshaw A, Hernon C.
Arch. Dis. Child. Fetal Neonatal Ed. 2003; **88**: F185-F189.

Immunologic memory in *Haemophilus influenzae* type b conjugate vaccine failure. McVernon J, Johnson P D R, Pollard A J, Slack M P E, Moxon E R.
Arch. Dis. Child. 2003; **88**: 379-383.

Severe visual impairment and blindness in children in the UK. Rahi J S, Cable N, on behalf of the British Childhood Visual Impairment Study Group (BCVISG).
Lancet 2003; **362** 1359- 1365.

Decline in mortality, AIDS, and hospital admissions in perinatally HIV-1 infected children in the United Kingdom and Ireland. Gibb D M, Duong T, Tookey P A, Sharland M, Tudor-Williams G, Novelli V, Butler K, Riordan A, Farrelly L, Masters J, Peckham C S, and Dunn D T. *BMJ* 2003; **327**: 1019 - 0.

Short-term risk of disease progression in HIV-1 infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. HIV Paediatric Prognostic Markers Collaborative Study Group. *Lancet* 2003; **362**: 1605-11.

Variations in initial assessment and management of inflammatory bowel disease across Great Britain and Ireland Sawczenko A, Lynn R, and Sandhu B K. *Arch. Dis. Child.* 2003; **88**: 990-994.

Features of inflammatory bowel disease in Great Britain and Ireland Sawczenko A, Sandhu B K
Arch. Dis. Child. 2003; **88**: 995-1000.

Renewing the Focus. HIV and other Sexually Transmitted Infections in the United Kingdom in 2002. London: Health Protection Agency, November 2003.

Estimating Hib vaccine effectiveness in England and Wales using the screening method. Ramsay ME, McVernon J, Andrews NJ, Heath PT, Slack MP. *J. Infect .Dis.* 2003; 188:481-5

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, McCartney AC. *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.
Sexually Transmitted Infections 2004; **80**: 159-166.

Appendix C Presentations 2003-2004

RCPCH Annual Scientific Meetings 2003 and 2004

The BPSU study of bilary atresia: outcome after 8 years: McKiernan PJ, Baker AJ, Mieli-Vergani G, Kelly D. York, April 2003. *Arch .Dis. Child.* 2003; **88** (Suppl 1): A13.

Internal abdominal injury due to child abuse – findings of the first year of a BPSU study. Barnes M, Sibert J, Norton CA, Kemp AM. York 2003 *Arch. Dis. Child.* 2003; **88** (Suppl 1): A33

Incidence of childhood stroke in the UK: Data from the British Paediatric Surveillance unit and the Strategic Health Authority. O'Callaghan FJK, William AN, Davis A, Kirkham FJ. York, April 2003. *Arch. Dis. Child.* 2003; **88** (Suppl 1): A35

Why is mother-to-child transmission of HIV infection still occurring in the UK and Ireland? Reported births 1998-2002. Tookey PA, Masters J, York, April 2003 (poster). *Arch. Dis. Child.* 2003; **88** (Suppl 1): A55

Changes in vertically acquired paediatric HIV in UK and Ireland over calendar time. Doerholt K, Duong T, Sharland M, Tookey P, Masters J, Gibb DM on behalf of CHIPS and NSHPC. York, April 2003. *Arch. Dis. Child.* 2003; **88** (Suppl 1): A56

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.

International Network of Paediatric Surveillance Units 3rd Conference Lisbon 2004

Invasive fungal infections in very low birthweight infants: United Kingdom national surveillance study. Clerihew L, 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

"What Causes Progressive Intellectual and Neurological Deterioration (PIND) in Children over 12 years old?" Verity C. British Paediatric Neurology Association Annual Meeting, Liverpool. 10-12 January 2003.

"Are children in the UK developing vCJD? The National Surveillance Study of Progressive Intellectual and Neurological Deterioration (PIND). Royal Australasian College of Physicians, Annual Spring Meeting, Hobart, Tasmania. Verity C. May 2003.

Uninfected infants born to HIV infected women. Hankin C, Tookey PA, Lyall H, Peckham CS. MRC London, May 2003 (poster).

Direct estimates of HIV prevalence among adults in England and Wales from a Bayesian multi-parameter synthesis: preliminary results for 2001. Goubar A, Ades AE, De Angelis D, Gill N, Fenton K, McGarrigle C, Mercer CH, Cliff S, Tookey P, Payne L, Hope V. MRC London, May 2003 (poster)

Surveillance of Haemolytic Uraemic Syndrome in the UK and Ireland (1997-2001) Using the BPSU methodology. Adak GK, Lynn RM, Taylor CM, Smith HR, O'Brien SJ, Locking M, Coia JE, Reily WJ. World VTEC Conference. Edinburgh, June 2003.

Childhood Stroke in the United Kingdom and Eire - a descriptive epidemiological study. Williams A, Kirkham F. Stroke Association Meeting Aston University. September 2003.

The condition: Epidemiology and Natural History. Heath PT. National Screening Committee workshop on Group B Streptococcus. London, November 2003.

"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.

Follow up of children exposed to antiretroviral therapy in pregnancy (CHART): a role for HIV Physicians? BHIVA Conference Cardiff 2004 (poster). Hankin CD, Tookey PA, Lyall EGH, Peckham CS. *HIV Medicine* July 2004 (in press).