INOPSU

International Network of
Paediatric Surveillance Units

First Progress Report 1999–2002

Membership

Australia
United Kingdom
Canada
Germany
Greece/Cyprus
Republic of Ireland
Latvia
Malaysia
Netherlands
New Zealand
Papua New Guinea
Portugal
Switzerland
Wales

Associate Membership

British Ophthalmic Surveillance Unit

INoPSU Secretariat 2000-2004

Convenor: Elizabeth Elliott (Australia)
Chris Verity (UK)
Richard Lynn (UK)
Rudi von Kries (Germany)
Nigel Dickson (NZ)

A tribute to Dr Victor Marchessault

Victor Marchessault was a paediatrician with great vision and intellect. He was a clinician, researcher, leader, and advocate for paediatrics and Child Health. In addition to his roles as Professor of Paediatrics and Infectious Diseases at the University of Ottawa and as Executive Vice-President of the Canadian Paediatric Society, he made a significant contribution to the surveillance of rare diseases in children. Victor played the major role in the development of the Canadian Paediatrician Surveillance Program in 1996 and forged close links between that unit and the units in Britain, Australia and elsewhere. He was a key player in developing a proposal for formation of the International Network of Paediatric Surveillance Units, which came to fruition in 1998. He was a member of the INoPSU Executive from 1998 and was unanimously elected to become Convenor of INoPSU in 2002. He was due to take up this position in 2003. The network will miss his leadership and commitment - he will be hard to replace. We will also miss Victor's personal qualities: his enthusiasm, integrity and hard work, his compassion and commitment, his friendship and his ready smile.

Contents

Foreword

The International Network of Paediatric Surveillance Units (INoPSU) is a truly collaborative organisation. Established in 1998, it joins 14 diverse countries with a common purpose - to conduct surveillance of uncommon conditions of childhood. The member units span the globe - from the Netherlands to Papua New Guinea to New Zealand. All use the active, monthly, surveillance method developed by Susan Hall and the British Paediatric Surveillance Unit in 1986.

The hallmark of these units is that they involve paediatricians in research. Child health specialists run most studies. Most results are reported at paediatric meetings and in paediatric journals. Thus, paediatricians feel an 'ownership' of these units and, as a result, the return of monthly report cards is remarkably high.

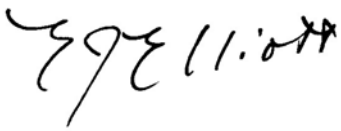
Collectively, INoPSU members conduct surveillance in a population of over 46 million children. More than 8000 clinicians report each month and the average response rate is over 90%. Over 180 conditions have been studied, from vaccine-preventible diseases through injuries, infections, rare syndromes and genetic diseases. More recent studies have linked the laboratory with the population to describe the molecular epidemiology of disease - Rett syndrome is one such example. The British search for cases of variant Creutzfeld Jacob Disease is an example of how units can respond to the public health need for monitoring emerging diseases. For many conditions studied, our surveillance units provide the only available national, prospective data. Many studies have generated hypotheses, fostering further research.

INoPSU provides a unique opportunity for collaborative research. Consultation encourages units to use the same diagnostic criteria for conditions studied. Simultaneous conduct of studies allows comparison of data between countries for conditions such as perinatally acquired HIV infection, vitamin K deficiency bleeding and early onset eating disorder. INoPSU also allows member units to critically evaluate surveillance methodology and to address current issues such as confidentiality in research.

Importantly, INoPSU has a major role in education, through dissemination of results in the medical press and the media. Lack of long-term funding to support unit infrastructure remains a problem for many INoPSU members. It is up to us to produce high quality data to convince governments and granting bodies of the worth of our units.

INoPSU functions predominantly as a virtual network and I invite you to visit us at www.inopsu.com. However, we are indebted to those who have made it possible for members to meet in person: the Canadian Paediatric Society and Health Canada (Ottawa 2000) and the Royal College of Paediatrics and Child Health (York 2002).

In closing, I must acknowledge the contribution made by Richard Lynn and Greta Ridley to the preparation of this first INoPSU progress report and pay tribute to Angus Nicoll, the first INoPSU Convenor and to the INoPSU Executive. I look forward to meeting you all again in Portugal in 2004!



Elizabeth Elliott (INoPSU Convenor 2000-2004)

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, in 1986 the British Paediatric Surveillance Unit (BPSU) initiated surveillance of rare paediatric disease. The success of the BPSU and the methodology it adopted quickly led to the establishment of other national units. This led to the potential of multi-national surveillance of such rare disease.

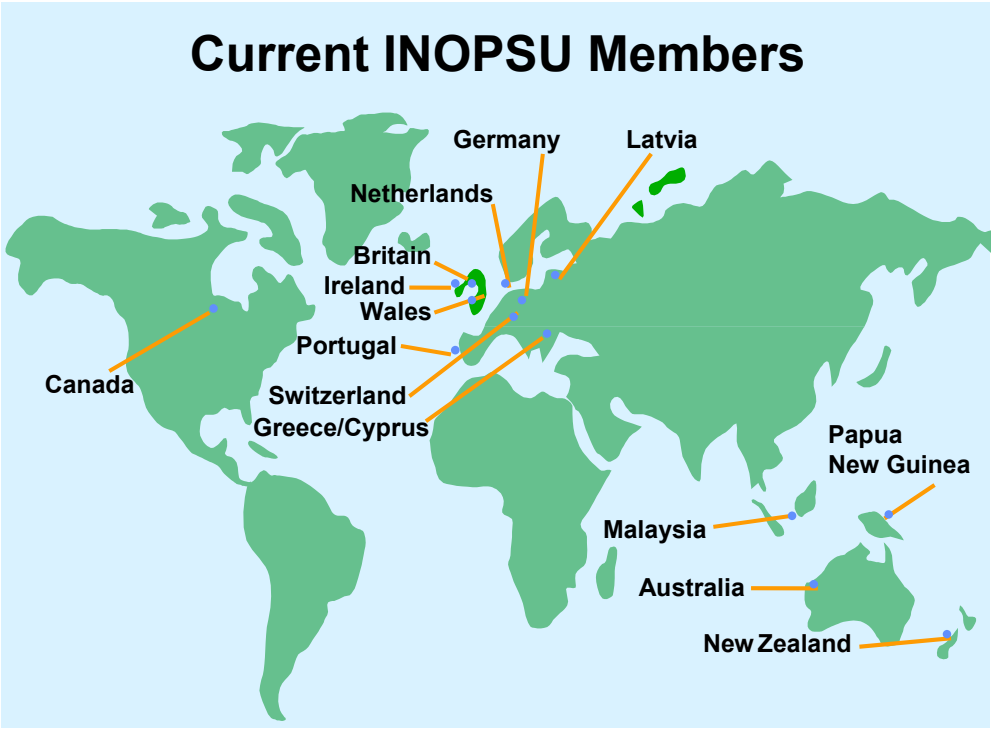
Initial discussions to develop the International Network of Paediatric Surveillance Units (INoPSU) began in 1996 following successful collaborations between the existing European Units. In 1998 a framework for such a network was developed and in the year 2000 it was officially launched in Ottawa, Canada at the first INoPSU scientific conference. The mission aim of the Network is 'the advancement of knowledge about rare and uncommon childhood infections and disorders through the participation of paediatricians in surveillance on a national and international basis'.

To achieve its mission aim, the Network's main concern is that of epidemiological surveillance, 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).

At its launch in 2000, there were ten founding paediatric surveillance units; from Australia, British Isles, Canada, Germany, Latvia, Malaysia, New Zealand, Netherlands, Papua New Guinea and Switzerland. Wales, Portugal, the Republic of Ireland, Greece and Cyprus have since joined them.

Between them, these units involve over 8000 clinicians in the surveillance of rare paediatric disorders, covering a child population of over 40 million. To date these units have helped to facilitate research into over 180 disorders.

This, the first annual report of the INoPSU, will outline the development of the Network and, by highlighting its activities from its inception, will demonstrate the potential for such a Network.



2 Background

History

The origins of the first national paediatric surveillance unit, the British Paediatric Surveillance Unit (BPSU), can be traced back to 1979. Attempts by the British Paediatric Association and the Health Protection Agency (formerly the Public Health Laboratory Service) in that period relied on passive reporting to undertake surveillance of Reye's syndrome, Kawasaki disease, haemolytic uraemic syndrome and haemorrhagic shock syndrome. Paediatricians were asked to remember and report cases of rare conditions when they were diagnosed. This met with only relative success and led to the development of an active alternative, sending paediatricians monthly reminders of the condition they were being asked to report. This system was officially launched in 1986 as a joint initiative between the British Paediatric Association (now the Royal College of Paediatrics and Child Health), the Institute of Child Health (London) and the Health Protection Agency. Over the following 15 years the BPSU has facilitated surveillance of over 50 rare disorders, including Reye's syndrome, HIV/AIDS and variant Creutzfeldt Jacob Disease (vCJD). The successful methodology of circulating a monthly report card to all consultant paediatricians in the United Kingdom and the Republic of Ireland was the basis for that now used by all the current members of INoPSU.

The aims, developed by the BPSU, have been incorporated by the other national surveillance units, and are:

- To facilitate research into uncommon paediatric disorders of public health importance for the advancement of knowledge and the improvement of prevention, treatment and service planning.
- To increase the awareness of the less common disorders of childhood among paediatricians.
- To respond rapidly to public health emergencies.

Establishment of an International Network of Paediatric Surveillance Units

The national and international recognition of the work of the BPSU led to enquiries from other national paediatric associations and in 1992 similar such units were launched in Germany, the Netherlands and Australia.

From very early on, the European units met informally to discuss research protocols and funding issues. Supported in 1995 by the establishment of the Swiss Unit, the European group met in Leiden, Netherlands to discuss joint surveillance of paediatric disorders and the need to seek funding from the European Union. Though the latter has been unsuccessful, several joint studies have been undertaken, namely in vitamin K deficiency bleeding, *haemophilus b* influenzae and childhood diabetes. These have led to the publication of several leading papers and presentations.

During this time the BPSU continued to have close ties with the Australian Paediatric Surveillance Unit (APSU) and the newly formed Canadian surveillance programme. With the support of the APSU, units in Malaysia, Papua New Guinea and New Zealand were formed in the mid 1990s. At the same time the Irish Paediatric Surveillance Unit (covering Northern Ireland and the Republic of Ireland) and the Welsh Paediatric Surveillance Unit were also being established. Though using the same methodology, their remit is slightly different in that they survey more common childhood disorders.

It became clear that even though representatives from each of the Units were meeting occasionally there was a need for an International Network of Paediatric Surveillance Units (INoPSU) to formalise the links among units. A proposal for INoPSU was drawn up in 1996 and ratified at the 22nd International Congress of Paediatrics held in Amsterdam, the Netherlands in August 1998.

The first INoPSU conference held in Canada in June 2000 confirmed the establishment of the network with the publication of the Amsterdam–Ottawa Note. Angus Nicoll was elected Convenor in 1998 and Elizabeth Elliott in 2000.

Mission and Aims of INoPSU

The Amsterdam-Ottawa Note laid down the mission of INoPSU that being "the advancement of knowledge about rare and uncommon childhood infections and disorders through the participation of paediatricians in surveillance on a national and international basis". INoPSU's primary aim is to facilitate communication and co-operation among national paediatric surveillance units (and researchers who use these units), and to assist in the development of new and existing units. INoPSU's aims are detailed in Table 1 overleaf. Communication is enhanced by the establishment of the INoPSU website http://www.inopsu.com. It links websites of individual units and various national paediatric bodies to facilitate the sharing of information on methodology, evaluation and ethical issues, and data derived from studies. The simultaneous collection of identical data in different countries also allows comparisons to be made of disease incidence, management and outcome among geographic regions. INoPSU also aims to develop uniform diagnostic criteria, disseminate new knowledge and enhance the ability to mount international surveillance of emerging disorders rapidly.

Table 1 Mission and Aims of INoPSU

Mission

The advancement of knowledge about rare and uncommon childhood infections and disorders through the participation of paediatricians in surveillance on a national and international basis.

Aims

To encourage and facilitate:

- communication and co-operation between existing Units
- development of new and existing Units
- information sharing about the surveillance process and methods such as study selection, data validation, statistical techniques, surveillance methodology and evaluation, including development of an INoPSU website
- peer-review and evaluation of ethics and confidentiality issues
- simultaneous or sequential collection of comparable epidemiological and clinical data in two or more nations
- national comparisons of incidence estimates for selected rare disorders of childhood
- dissemination of information to national and international health authorities in order to raise awareness, encourage early diagnosis and management of rare conditions
- identification of emerging disorders
- establishment of international cohorts which could potentially support future research
- development and clarification of internationally recognised diagnostic criteria
- dissemination of new knowledge to the general public and others, e.g. parent support groups
- prompt response to international emergencies relating to emerging rare childhood conditions

INoPSU Structure

INoPSU's founding members are listed in Table 2 opposite. An elected secretariat oversees the INoPSU, undertaking regular consultation with units and seeking funding as necessary. An 'international link person' has been nominated from each Unit. INoPSU functions primarily as an electronic network. An INoPSU website (http://www.inopsu.com) has been developed linking the websites of the individual units. Richard Lynn at the British Paediatric Surveillance Unit (BPSU) initially acted as the INoPSU secretariat and the APSU administers the website. These duties were due to transfer to the Canadian Paediatric Surveillance Programme in April 2003. However, following the untimely death of the convenor elect Professor Victor Marchessault, a decision to do so will not be made until the 3rd INoPSU conference in April 2004.

Most national units are affiliated with their country's professional paediatric organisation and various other organisations concerned with child and public health are frequently represented on units' administrative boards. Staffing levels are variable depending on the size of the Unit and available funding.

Table 2a Founding Members of INoPSU

Founding Member	Year Established	Affiliations	Staffing Salaried FTE*
Australian Paediatric Surveillance Unit	1992	Division of Paediatrics, Royal Australasian College of Physicians Centre for Disease Control, Department of Health and Aged Care	1.8
British Paediatric Surveillance Unit	1986	Royal College of Paediatrics and Child Health Health Protection Agency Institute of Child Health, London. Scottish Centre for Infectious and Environmental Health Faculty of Paediatrics, Royal College of Physicians (Ireland)	1.5
Canadian Paediatric Surveillance Program	1996	Canadian Paediatric Society Centre for Infectious Disease Prevention and Control, Health Canada	2.0
German Paediatric Surveillance Unit	1992	German Paediatric Association	1.0
Latvian Paediatric Surveillance Unit	1996	Latvian Paediatric Association	1.0
Malaysian Paediatric Surveillance Unit	1993	Malaysian Paediatric Association	1.0
Netherlands Paediatric Surveillance Unit	1992	Dutch Paediatric Association	0.6
New Zealand Paediatric Surveillance Unit	1997	New Zealand Paediatric Society New Zealand Ministry for Health	0.5
Papua New Guinea Paediatric Surveillance Unit	1996	Paediatric Society for Papua New Guinea HOPE worldwide (PNG branch)	0.5
Swiss Paediatric Surveillance Unit	1995	Swiss Federal Office of Public Health Swiss Paediatric Society	0.3

*FTE = full time equivalent.

Table 2b Recent Members to INoPSU

Recent Members	Year Established	Affiliations	Staffing Salaried FTE*
Welsh Paediatric Surveillance Unit	1994	Welsh Paediatric Society	0.2
Irish Paediatric Surveillance Unit	1996	Irish Paediatric Association, Ulster Paediatric Society	<1.0
Portuguese Paediatric Surveillance Unit	2001	Portuguese Paediatric Association	<0.5
Greece/Cyprus Paediatric Surveillance Unit	2002		<1.0

3 How the Surveillance System Works

The methodology used by paediatric units provides a mechanism for effective ascertainment of cases of rare or uncommon conditions. It can be characterised as an efficient postal system which, by the use of a monthly mailing card, allows the simultaneous and efficient conduct of multiple surveillance projects whilst limiting the burden of reporting for individual doctors. Individuals or organisations are able to apply to use surveillance units to conduct a study.

Selection of studies

All existing units have adopted a similar selection procedure in order to identify studies for inclusion in their respective reporting system. Applications to conduct a study are considered by the scientific panel overseeing the running of the surveillance unit. This panel will normally comprise of paediatricians (general and specialist), epidemiologists and specialists in public health. Applications need to outline the research aims of the study, the diagnostic criteria to be adopted, and practicalities on how the study is to be administered and funded. To be approved for study, conditions must fulfil certain criteria (see box). Importantly, before a study can be approved, it must conform to international ethical guidelines (International Ethical Guidelines for Biomedical Research Involving Human Subjects prepared by the Council for International Organisations of Medical Sciences and the World Health Organisation in 1993).

For a number of reasons it may be considered that the surveillance mechanism is not suitable for answering the objectives of a proposed study. The condition may be too common and therefore place too great a burden on paediatricians for reporting or follow-up; there may be no suitable case definition; the aim of the study may be to collect a cohort for further unspecified research or the investigation may constitute audit rather than surveillance. If a study is not accepted, the panel advises the applicant on alternative means of undertaking the work.

Though considered stringent, the advantages of this procedure are two-fold. Firstly, respondents know that a study must be methodologically sound to be accepted by the surveillance unit. Secondly, prospective investigators know that if a study is accepted they are assured of a high level of involvement from clinicians.

Once accepted, studies are usually included in the reporting mechanism for a period of one to three years. Study duration may be extended if the condition is deemed of particular public health significance (e.g. vCJD), if it is a condition of very low frequency (e.g. congenital rubella) or when the paediatric surveillance unit is the optimal mechanism for gathering routine surveillance data (HIV and AIDS).

The reporting system

Factors that favour acceptance

- Scientific importance.
- Rarity of the condition, though short-term or geographically limited studies of commoner disorders are considered.
- Proposals with study outcomes of clear importance to public health.
- Uniqueness, priority will not be given if similar studies have recently been undertaken or if other data sources are readily available (although the investigators are encouraged to use alternative data sources for validation and completeness of reporting).
- Attention to detail, in terms of clear achievable objectives, practicability, patient confidentiality and resources.
- Practicality and limited workload for reporting paediatricians.
- Ethics approval.

All INoPSU members undertake “active” surveillance, in which the initiation for notification comes from the Unit rather than the clinician (“passive”). Active surveillance results in considerably higher case ascertainment than passive surveillance, and minimises recall bias. The methodology varies slightly among INoPSU units to suit local conditions. Each month, all clinicians participating in the scheme are sent a card listing the conditions currently under surveillance. Figure 1 shows a sample card from the BPSU.

Figure 1

British Paediatric Surveillance Unit Report Card

NOTHING TO REPORT **June 2003 [203-06]**

Specify in box number of cases seen **CODE No [ ]**

HIV & AIDS

Progressive Intellectual & Neurological Deterioration

Congenital Rubella

Suspected Fatal Adverse Drug Reactions

Congenital Toxoplasmosis

Severe Complications of Varicella

Invasive fungal infections in VLBW infants

Severe Hyperbilirubinaemia in the newborn

Langerhans Cell Histiocytosis

A set of instructions for completing the card, including case definitions of the conditions listed on the card is also circulated. Before a new study begins, the mailing list also receives a specially produced study protocol card, a case definition and other information about the study.

Respondents are asked to return the card to the surveillance unit, indicating on the card the number of cases of each condition that they have seen during the preceding calendar month *or* that they have nothing to report. When reporting a positive case, respondents are also asked to make a note of the condition and keep patient details for future reference.

Participants are expected to return cards even if they have *no* cases to report - and for this purpose 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 and provides an estimate of how many cases might have been missed. Reminders are sent to all participants in the scheme who do not regularly return their card. Using this system overall, compliance rates are continually monitored.

Some units use a reply paid report card, and email reporting was introduced in Australia in 1997. Telephone and facsimile reporting is requested for some studies when timely reporting is required (e.g. to facilitate the obtaining of biological specimens).

On receiving a case report, the surveillance unit 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, are clear and straightforward and are 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. In two units (Canadian Paediatric Surveillance Program and the New Zealand Pediatric Surveillance Unit) study questionnaires are sent directly to the notifying clinician from the unit for some studies.

The investigators subsequently report back to the surveillance unit on the outcome of each case, indicating when cases have been confirmed as meeting the case definition and identifying duplicate case reports. 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 2).

Workload and response rates

Mailing lists range in size from 40 to 2300 individuals, and include general and specialist paediatricians and non-paediatric specialists (paediatric surgeons and dermatologists). In Switzerland, Germany and Latvia, departmental heads rather than individual clinicians report on behalf of their colleagues. In developing the mailing list it is important it is as inclusive (hence representative) as possible, to maximise ascertainment. Surveillance covers the national population younger than 16 years of age, which ranges from 0.5 million in Latvia to 12.8 million in Britain/Ireland. Currently over 8000 paediatricians worldwide contribute monthly to the reporting of uncommon disease in a population of over 46 million. (Table 3 overleaf)

The return rate of monthly cards to units ranges from 30% to 100% and that of questionnaires for individual studies ranged from 47% to 100%. The workload for most clinicians who participate in national surveillance of rare disease is low. In any single year a large proportion of clinicians on the mailing list do not report a single case and, hence, are not required to complete a questionnaire requesting further details. An evaluation of the reporting system undertaken by the Australian unit showed that clinicians perceived this method of surveillance to be simple and useful. The high return rate of monthly cards and questionnaires indicates acceptability by clinicians on the mailing list.

Figure 2

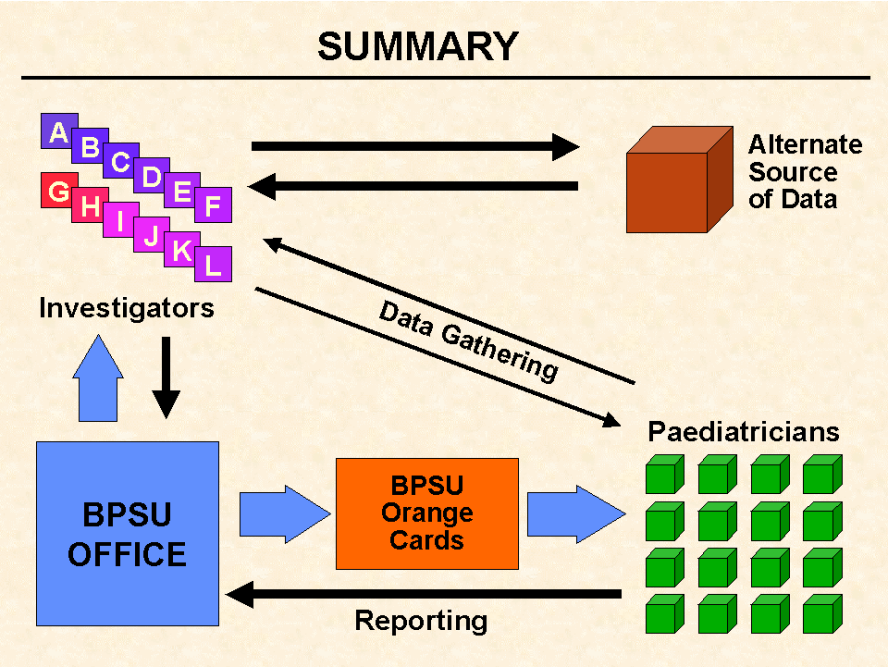


Table 3 Reporting mechanism

Country	Child Population (aged 0-15 years)	Respondents	Reply Paid Card	Report Cards Returned (%)	Questionnaire return rate (%)
Australia*	3.9	942	Yes	93	66-97
Britain/Ireland	12.8	2105	No	92	85-100
Canada	6.3	2294	Yes	86	90-100
Germany	12.0	468	No	95	47-100
Latvia	0.4	22	No	70	–
Malaysia	7.7	395	Yes	75	–
Netherlands	2.9	445	Yes	92	93
New Zealand	0.8	179	Yes	94	90
Papua New Guinea	2.0	40	Yes	73	–
Switzerland	1.3	40	Yes	100	96-98
Portugal	1.8	1500	Yes	30	60
Ireland~	1.3	135	Yes	75	85-90
Wales~	0.65	119	No	95	85

* Approximately 50% of clinicans participating in APSU surveillance reported by email in 2002.

~ Wales and the Republic of Ireland have their own surveillance unit looking at more common disorders, as well as being involved in the BPSU.

The need for complimentary data sources

Although desirable, full case ascertainment is not always achievable. Indeed, complete ascertainment is not always required to fulfil the aims of some studies, especially when the system aims to identify cohorts that are later invited to enter randomised control trials or clinical surveys. However, awareness of potential reasons for under ascertainment is important. This can be due to incompleteness of the mailing list, cases being seen by non-paediatricians, complicated case definitions or diagnostic difficulties.

Investigators are therefore encouraged to use other complimentary case sources to optimise ascertainment, provide validation and improve the accuracy of data collected.

Within the British Isles, national surveillance of HIV and AIDS in children has, for example, ascertained data via paediatricians, obstetricians, the national haemophilia network and microbiologists (Figure 3). Surveillance studies of *haemophilus influenzae*, haemolytic ureamic syndrome and group b streptococcal disease have also used laboratories to compliment their data capture. Other data sources have included death registers, birth defect registers and parent support groups.

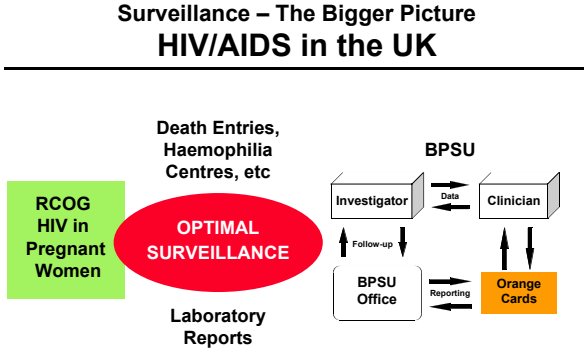
Multi-ascertainment also allows for the use of capture-recapture techniques to support surveillance, allowing estimation of the true frequency of disease in a population. Using these methods it has been shown that national surveillance units can ascertain between 75-95% of cases.

Funding

Units represent value for money as they can conduct up to 16 surveillance studies simultaneously. However, there are fixed costs which include postage and salaries. Most units are funded by a variety of government, charitable and commercial sources. The national health department is the predominant funding source in New Zealand, Switzerland and Britain and is a major contributor in Australia and Canada. In some countries, an investigator fee contributes towards infrastructure costs and ranges from EURO€110 to EURO €9800 per year.

As an organisation INoPSU receives no funding. Its activities are supported through the budgets of individual units. Health Canada and the Canadian Paediatric Society supported the first INoPSU conference and the second received grants from the Wellcome Trust, Wyeth Vaccines and the Royal College of Paediatrics and Child Health.

Figure 3



4 Surveillance Activities

The value of individual units and of INoPSU will be measured in several ways, including their ability to:

- raise awareness of rare paediatric disease through education of health professionals and the lay public
- contribute new information about rare diseases
- inform public health policy, research and resource allocation.

Individually, the national surveillance units have already demonstrated their educational impact. This has been achieved by the dissemination of information via newsletters, annual reports, presentations to scientific meetings and publications in the scientific literature (see Appendices 1 and 2).

In the APSU evaluation, the majority of clinicians said provision of diagnostic criteria and information derived from studies was educationally useful and 33% said such information had informed or changed their clinical practice. The increase in reports of Kawasaki disease in the British Isles during 1986-7 was attributed not to a true increase in incidence but to the newly established active reporting system of the BPSU, which increased clinicians awareness of the diagnostic criteria for this condition. A similar phenomenon occurred in Australia when congenital and neonatal varicella became notifiable to the APSU.

The development of the INoPSU website in 2000 <www.inopsu.com> (see over page) has raised the profile of the Network further, allowing professionals and the general public access to information on the studies being conducted, either individually or jointly, by Units.

Many studies by units have impacted on public health by monitoring outcomes of national vaccination programs, late sequelae of vaccination, or incidence of vaccine-preventable conditions prior to the availability of vaccination. These studies include surveys of congenital rubella, subacute sclerosing panencephalitis, meningoencephalitis after measles mumps rubella vaccination, acute flaccid paralysis and *haemophilus b influenzae (Hib)* vaccine failures, the latter being part of a collaborative Dutch/British surveillance.

Units also have the ability to respond rapidly to public health emergencies. Several units have assessed the impact of changing the route of administration of vitamin K prophylaxis on the incidence of vitamin K deficiency bleeding in the newborn.

Five units (Australia, Britain, New Zealand, Canada and Portugal) have monitored the association between haemolytic uraemic syndrome and Shiga toxin-producing *E.coli* and comparative data was presented at the second INoPSU conference.

The recent identification of variant Creutzfeld Jacob Disease in Britain has led to monitoring of the incidence and aetiology of progressive intellectual and neurological degeneration in childhood.

Studies have also informed public health policy.

1. Studies of HIV/AIDS and perinatal exposure to HIV have provided information on perinatal transmission of HIV and the role of screening and treatment in pregnancy.
2. Studies on toxoplasmosis and neonatal herpes simplex virus infection concluded that universal screening in pregnancy was not warranted due to insufficient case frequency.
3. A repeat warning of the danger of using aspirin in childhood was issued after the BPSU study on Reye's syndrome described the continued association between aspirin use in children and this disorder.
4. Some studies have allowed evaluation of prevention strategies, such as pool fencing.
5. Some studies have identified potential risk factors, e.g. epilepsy for drowning or being the child of an immigrant (unvaccinated) parent not vaccinated for congenital rubella.
6. Data from the BPSU study on chemistry set poisoning supported data which led to changes in European Union law regarding the packaging of children's toys.
7. Some studies e.g. Rett Syndrome have provided insight into the molecular epidemiology of disease and phenotype-genotype correlation and have identified cohorts for future research, including randomised clinical trials of novel treatment.
8. Studies have also provided information on current management strategies, e.g. use of immunoglobulin in Kawasaki disease and the usefulness of a pilot neonatal screening program for congenital adrenal hyperplasia.

Data from studies has also allowed validation of diagnostic criteria, documentation of short-term outcome and description of the clinical spectrum of disease. The Dutch, British and German units have collaborated on surveillance of insulin dependent diabetes mellitus in the under fives, while the Dutch and British Units collaborated on a study on Hib vaccine failures. Use of several Australian study protocols (haemolytic uraemic syndrome, congenital rubella, acute flaccid paralysis, HIV/AIDS, neonatal herpes simplex virus infection and vitamin K deficiency bleeding)

by New Zealand researchers allows international comparison of data.

The exciting potential for simultaneous study of a single condition by all INoPSU member countries also exists.

The examples above demonstrate the impact that national surveillance units and their studies have had in informing public health professionals and their practice. The methodology developed by the BPSU broke new ground and has been adapted for use elsewhere. INoPSU has built on the strength of individual units and provides a unique mechanism for international collaborations. To date in total 180 conditions have been studied (Table 4 and Appendix 3), leading to the reporting of tens of thousands of cases. Two scientific conferences have been held by INoPSU and a third is planned in Portugal in 2004 and the number of countries showing interest involved in the international network continues to grow.

One of the main aims of INoPSU is to encourage the development of multi-national surveillance studies so that direct comparisons can be made between countries with diverse geographical and population characteristics. For this to be truly successful, we must develop study protocols that will allow universal implementation of studies and agree on appropriate case definition and questionnaires. Examples of where such data sharing and comparisons have taken place are illustrated in Chapter 6. As INoPSU matures its is hoped that surveillance can commence in tandem using agreed protocols. This with the development and use of uniform diagnostic criteria and the dissemination of new knowledge will ultimately be of benefit to children in paediatric care.

Figure 4 Website of International Network of Paediatric Surveillance Units

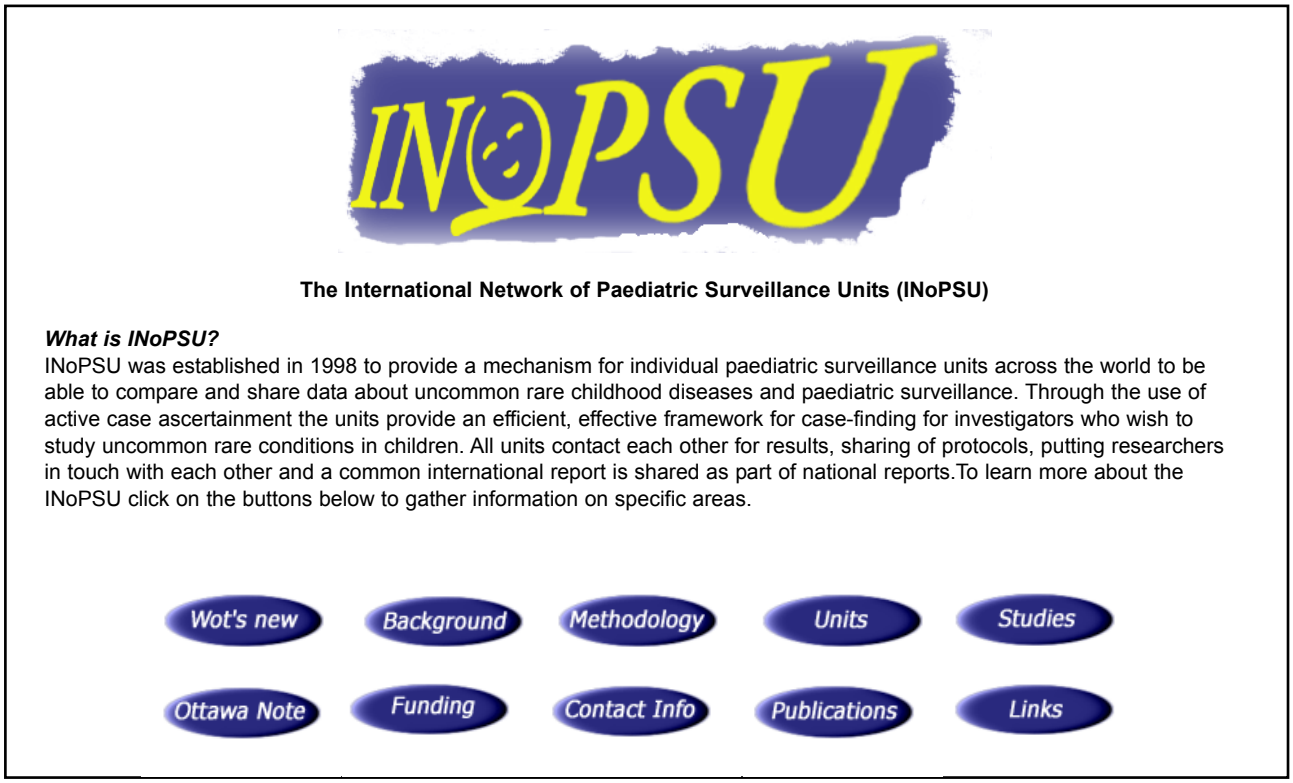


Table 4 Conditions under surveillance in 2001/2 by National Paediatric Surveillance Units and studies requesting biological specimens

CONDITION	UNIT PERFORMING SURVEILLANCE	
	STUDIES	SPECIMENS REQUESTED
Acute Flaccid Paralysis	APSU, CPSP, NSCK, NZPSU, PNGPSU, SPSU	APSU, CPSP, NZPSU, PNGPSU, SPSU
Aseptic Meningitis following measles, mumps, rubella vaccine	ESPED	
Acute Rheumatic Fever	SPSU	
Chronic Inflammatory Bowel Disease†	BPSU	
Coeliac Disease	LPSU, NSCK	LPSU
Congenital Adrenal Hyperplasia	NSCK	
Congenital Brachial Palsy	BPSU	
Congenital Cytomegalovirus Infection	BPSU	
Congenital Heart Disease	MPSU	
Congenital Hypothyroidism	PNGPSU	
Congenital Rubella	APSU, BPSU, CPSP, NZPSU, SPSU	CPSP, SPSU
Cystic Fibrosis	LPSU	
Duchenne Muscular Dystrophy	MPSU	
Encephalitis (3-36 months)	BPSU	BPSU
Facial Palsy	WPSU	
Fatal/near Fatal Asthma	MPSU	
Group B Streptococcal Infection	NSCK	
Haemolytic Uraemic Syndrome	APSU, BPSU* , ESPED, NZPSU, SPSU	APSU, BPSU, NZPSU
Vitamin K deficiency bleeding (including Haemorrhagic Disease of the Newborn)	APSU, CPSP, ESPED, NZPSU, SPSU	CPSP, SPSU
Hirschsprung Disease	APSU	
HIV/AIDS and/or Perinatal Exposure to HIV	APSU, BPSU, LPSU, MPSU, NSCK, NZPSU, PNGPSU	LPSU
Infants Hospitalised with Pertussis	ESPED, NSCK	
Idiopathic Thrombocytopenia	ESPED	
Insulin-Dependent Diabetes Mellitus	ESPED, LPSU, NSCK, PNGPSU, NZPSU, WPSU	LPSU
Invasive *Haemophilus Influenzae* Infection	APSU, BPSU, ESPED	APSU, BPSU
Ischaemic Stroke in Infants	ESPED	
Leukaemia	LPSU	LPSU
Lues Congenita	LPSU	LPSU
Multiple Sclerosis in Infants	ESPED	
Neonatal Abstinence Syndrome	WPSU	
Neonatal Fungal Septicaemia	ESPED	
Neonatal Herpes Simplex Virus infection	APSU, NZPSU, SPSU	
Neonatal Meningitis	MPSU	
Neural Tube Defects	NSCK, SPSU	
Neurological Endemic Cretinism	PNGPSU	
Organoacidopathies and Fatty Acid Oxidation Defects	ESPED	
Paediatric Malignancies ‡	PNGPSU	

Table 4 (cont.)

CONDITION	UNIT PERFORMING SURVEILLANCE	
	STUDIES	SPECIMENS REQUESTED
Physical Child Abuse	WPSU	ESPED
Pneumococcal 1 Sepsis/ Meningitis	ESPED	LPSU
Prader Willi Syndrome	ESPED	CPSP
Primary Immunodeficiency Disorders §	APSU	
Progredient Subacute Neurologic Diseases	LPSU	
Progressive Intellectual and Neurological Deterioration (including CreutzfeldJakob disease)	BPSU, CPSP	
Renal Tubular Acidosis	PNGPSU	
Retinopathy of Prematurity (stage III and beyond)	NZPSU	
Reye's Syndrome	BPSU	CPSP, PNGPSU
Rotavirus Infection	NSCK, SPSU	
Severe Combined Immunodeficiency	APSU	
Subacute Sclerosing Panencephalitis	APSU, BPSU, CPSP, PNGPSU	
Subdural Haematoma/Effusion (<2years)	BPSU, NZPSU	
Transient myeloproliferative Syndrome in newborns with Down Syndrome	ESPED	
Venous Thromboembolic Complaints	NSCK	

* Previously studied by the BPSU in 1986-9.

† Ulcerative colitis, Crohn's disease and intermediate colitis.

‡ Wilm tumour, Burkitt lymphoma, Leukaemia, Neuroblastoma, Lymphoma (non-Burkitt's), other.

§ Predominantly antibody defects (eg X-linked agammaglobulinaemia, IgA deficiency, IgG subclass deficiency); Combined immunodeficiencies (eg severe combined immunodeficiency, common variable immunodeficiency); Immunodeficiencies with other major defects (eg Wiscott-Aldrich syndrome, Di George syndrome, Ataxia telangiectasia); Complement deficiencies, including C1 esterase inhibitor deficiency (eg hereditary angioneurotic oedema); Defects of phagocytic function (eg chronic granulomatous disease, leukocyte-adhesion deficiency, Schwachman syndrome); other.

5 Reports from the National Paediatric Surveillance Units

Australian Paediatric Surveillance Unit (APSU)

The APSU was formed in 1992 and commenced surveillance in May 1993. It is a Unit of the Royal Australasian College of Physicians. The APSU currently surveys approximately 1042 clinicians in child health on a monthly basis, covering a child population (<15 years) of 3.9 million. The current return rate for monthly report cards is 96% and for completed questionnaires is 86%. The APSU introduced email reporting in 1997 and currently 52% (538) of clinicians have elected to use this method of reporting.

Currently 16 studies are conducted simultaneously. Studies that commenced in 2001 include adverse effects from complimentary or alternative medicine, fetal alcohol syndrome and infants hospitalised with pertussis. Studies that were completed in 2001 include haemolytic uraemic syndrome (December 2001), congenital and idiopathic nephrotic syndrome (June 2001), severe combined immunodeficiency syndrome (December 2001) and infants hospitalised with pertussis (December 2001). Other studies currently under surveillance include acute flaccid paralysis, CHARGE Association, congenital cytomegalovirus infection, congenital rubella infection, HIV/AIDS and perinatal exposure to HIV, Munchausen syndrome by proxy, neonatal herpes simplex virus infection, Rett syndrome and vitamin K deficiency bleeding. Conversion disorder and early onset eating disorders were approved for study in 2002.

In 2001, the APSU provided clinical and diagnostic information to a number of Public Health organisations. The APSU investigators participated in a national review of fetal alcohol syndrome conducted by the National Expert Advisory Committee on Drugs and Alcohol. Investigators of the study on infants hospitalised with pertussis contributed to a workshop in Sydney on Pertussis in Adolescents and Adults. Investigators on the acute flaccid paralysis study contributed data to the WHO and to a national workshop on containment of polio virus and surveillance for poliomyelitis. Data from the primary immunodeficiency disorders study has been included in the national Primary Immunodeficiency Register.

Studies through the APSU have given rise to more than 108 publications including peer-reviewed articles, research reports and published abstracts and a wide range of presentations (102) that have informed the general public and the wider medical community. The APSU's most recent publication, "The Australian Paediatric Surveillance Unit Progress report" which is currently in press in the Journal of Paediatrics and Child Health, provides a surveillance overview of the APSU and discusses study results to date.

The APSU updates paediatricians with quarterly bulletins that include current study profiles and also provides the Bulletin of Royal Australasian College of Physicians (RACP news) with regular updates. Information on the ASPU may be accessed through the APSU website (http://apsu.inopsu.com). APSU personnel have been responsible for developing websites for INoPSU (http://www.inopsu.com) and assisted in the development of the BPSU website (http://bpsu.inopsu.com).

The APSU currently receives its major funding from the Federal Department of Health and Aged Care. Individual studies have been sponsored by Roche (vitamin K deficiency bleeding), GlaxoSmithKline (infants hospitalised with pertussis) and Healthways (fetal alcohol syndrome).

APSU continues to maintain close links with INoPSU members. Currently Associate Professor Elizabeth Elliott is the Convenor of INoPSU.

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British Paediatric Surveillance Unit (BPSU)

The BPSU commenced surveillance in 1986 and is the longest running of the existing national surveillance units. During this time it has established a long and admirable track record in the study of uncommon childhood illness. It is a joint project of the Royal College of Paediatrics and Child Health, the Health Protection Agency and the Institute of Child Health, with support from the Scottish Centre for Infection and Environmental Health and the Royal College of Physicians of Ireland. Over the period of 17 years it has facilitated surveillance of over fifty rare disorders. The BPSU currently sends its monthly orange card to over 2100 paediatricians and specialist clinicians in the United Kingdom and the Republic of Ireland, covering a child population of nearly 13 million. Compliance in returning the orange card and questionnaires is excellent at around 92%.

In 2001, five studies came to an end, haemolytic uraemic syndrome, group b streptococcal disease, and encephalitis in early childhood, Reye's syndrome and subacute sclerosing panencephalitis. The latter two conditions had been on the card since 1986. Five studies commenced in 2001, namely vitamin K deficiency bleeding, cerebral vascular disease/stroke and like illness, congenital cytomegalovirus infection, thrombosis in childhood and internal abdominal injury due to child abuse. Studies also undertaken in 2001 include HIV/AIDS, congenital rubella infection, and progressive intellectual neurological deterioration (including vCJD).

In 2002 three studies commenced, fatal adverse drug reactions, severe complications of varicella infection and congenital toxoplasmosis. Studies on invasive fungal infections in low birth weight infants, Langerhans cell histiocytosis and congenital neonatal herpes simplex virus have been approved to commence in 2003.

The Department of Health, by awarding the Unit a further 3-year grant to 2004, suitably acknowledges the work of the BPSU. This past year also saw the revamping of the BPSU website (http://bpsu.inopsu.com) and much thanks should go to our colleagues in Australia who greatly assisted.

Some highlights of the Unit's work over the past fifteen years include the confirmation of an association between aspirin and Reye's syndrome; identification of the under-recognition of Kawasaki disease; confirmation of the link between *E.coli* O157 and HUS in the UK. In addition the Unit has undertaken the first national surveillance of inflammatory bowel disease; addressed the impact of changing management with regard to vitamin K prophylaxis and identified concerns over the packaging of toy chemistry sets - leading to a change in European law. Over 200 papers arising from BPSU studies have been published in peer review journals and many presentations across the globe have been given.

Perhaps of most importance, the BPSU has shown that the methodology used is a reliable and effective way of collecting data. This is confirmed by the replication of this system by other specialist groups within the United Kingdom and by other paediatric groupings across the world.

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Canadian Paediatric Surveillance Program

The Canadian Paediatric Surveillance Program (CPSP) started in 1996 as a joint project of the Canadian Paediatric Society (CPS) and Health Canada's Centre for Infectious Disease Prevention and Control. From three studies in the inaugural year to nine studies in 2001, today nearly 2350 paediatricians and paediatric sub-specialists participate monthly and achieve a 95% response rate for completing detailed case questionnaires. The Canadian paediatric population under the age of 18 years is 6.3 million.

Three studies concluded in 2001 – anaphylaxis, cerebral oedema in diabetic ketoacidosis and progressive intellectual and neurological deterioration, and two were added – CHARGE association/syndrome and necrotising fasciitis. Other current studies included – acute flaccid paralysis, congenital rubella syndrome, haemolytic uraemic syndrome, hepatitis C infection, neonatal herpes simplex virus infection, neonatal liver failure/perinatal haemochromatosis and Smith-Lemli-Opitz syndrome. In total 19 studies have been facilitated through the Program.

For 2002, the CPSP Steering Committee approved new studies on vitamin D dependent rickets and severe hyperbilirubinemia in the newborn and is considering proposed studies on severe adverse drug reactions, autism and Prader-Willi syndrome.

No surveillance programme would be complete without timely feedback to its participants. So in 2001, the CPSP concentrated on promoting the programme and increasing communication to its participants and the general public. A series of publications followed including educational resources, abstract and poster presentations, updates in the CPS News, monthly highlights in the CPS Journal: Paediatrics & Child Health, culminating with the May/June issue dedicated to surveillance. The bilingual CPSP website was updated in-house and will be up and running early in 2002. The CPSP also continues to participate actively in INoPSU.

The CPSP is most encouraged by the recent trend of an increased level of support from CPS expert committees, national paediatric sub-speciality associations, chronic-disease family support groups, various departments within Health Canada and paediatric hospital research foundations. This is a manifestation of how the CPSP is building recognition within the Canadian research community.

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German Paediatric Surveillance Unit (ESPED)

Encouraged by the success of the BPSU, a German adaptation of the surveillance scheme called the ESPED was initiated in July 1992 to cover a country which has one of the largest child populations of any of the units (around 12 million). The surveillance system differs from the original British methodology in that monthly report cards are sent to paediatric department heads rather than individual paediatricians. The response rates for the 452 groups of clinicians have risen significantly from 55% in 1992 to 98% in 2001, with the follow-up rate of completion of questionnaires in the range of 47 to 100%.

A number of studies have been completed. These include Reye's syndrome, Ondine's curse (primary failure of respiratory regulation), Kawasaki disease, acute renal failure and acute liver failure, haemolytic uraemic syndrome, HSES, fatal/near fatal asthma and neonatal infection due to fungi (candida).

In 2001 the conditions under surveillance were:

Diabetes mellitus under 5 years / insulin-dependent diabetes mellitus, steroid-resistant nephrotic syndrome, Invasive group B streptococcal disease, invasive haemophilus influenzae infections (all types), idiopathic juvenile osteoporosis, kernicterus, imported tropical diseases (malaria, schistosomiasis, leishmaniasis), neonatal sinus venous thrombosis, ingestion of lamp oil (intoxications), pneumococcal sepsis/meningitis, RSV disease requiring intubation and artificial ventilation, intersexuality and severe genital malformations, transient myeloproliferative syndrome in neonates with Down-Syndrome, haemorrhagic disease of the newborn (vitamin K deficiency bleeding), glucose transporter defect (GLUT1).

The study of *Haemophilus influenzae* type b disease: demonstrated the impact and effectiveness of diphtheria-tetanus toxoids-acellular pertussis (inacitvated poliovirus) / *H. influenzae* type b combination vaccines.

Schmitt H-J, von Kries R, Hassenpflug B, et al. Haemophilus influenzae type b disease: impact and effectiveness of diphtheria-tetanus toxoids-acellular pertussis (inactivated poliovirus) / H. influenzae type b combination vaccines. Pediatr Infect Dis J 2001; **20(8):** 767-774.

New studies in 2002 include inherited hypocalemic salt-losing tubulopathies / Bartter-like syndromes and narcolepsy.

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Irish Paediatric Surveillance Unit (IPSU)

Set up in 1996 by the Faculty of Paediatrics of the Royal College of Physicians (Ireland) in cooperation with the Ulster Paediatric Society, the IPSU compliments the work of the British Paediatric Surveillance Unit by surveying for more common disease in North and South Ireland. Covering a child population of around 1.3 million, surveillance is achieved through a monthly-prepaid postcard circulated to around 150 members of the Irish Paediatric Society. The response rate is currently around 80%. Studies undertaken in 2001 include tuberculous meningitis, status epilepticus, coeliac disease, nephrocalcinosis, diaphragmatic hernia and neural tube defects.

In 2002 the IPSU was accepted as a full member of the INoPSU.

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Latvian Paediatric Surveillance Unit

The Latvian paediatric surveillance system began in 1997 and conducts active surveillance using a mailed report card. Latvia has a child population of 429,000 and there are only two major children's hospitals in Latvia. Cards have been sent to comparatively few clinicians. Response rates in the past year are currently around 70%. In 2001 the following conditions were studied: congenital syphilis (4), Hodgkin's disease (10), Non-Hodgkin's lymphoma (7), diabetes mellitus (47), histocytosis X (2), aplastic anaemia (1), PKU (2), leukemias (24) and Reye's Syndrome (1), In 2000 two cases of haemolytic uraemic syndrome were seen but none were reported in 2001.

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Malaysian Paediatric Surveillance Unit (MPSU)

The MPSU was established in December 1993 and surveillance began in September 1994 under the auspices of the Malaysian Paediatric Association. It covers all of Malaysia with a child population of 7.6 million. The unit has adopted the classical BPSU methodology with cards being circulated to around 400 paediatricians and surgeons. The initial response rate is encouraging at 75%, having risen as the system becomes more familiar to respondents. Initially four conditions were under surveillance, paediatric HIV and

AIDS, neonatal meningitis, acute fulminant liver failure and death from asthma. 1998 saw the commencement of surveillance for Duchenne muscular dystrophy and in 1999 for neonatal congenital heart disease. However since then there have been financial problems that led to the system being suspended. The management of the Unit has recently undergone re-organisation and we hope to re-commence surveillance soon.

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Netherlands Paediatric Surveillance Unit (NSCK)

The Dutch Paediatric Surveillance Unit started surveillance in October 1992. It has a scientific board of eight clinicians, one co-ordinating paediatrician (0.2 FTE) and secretarial assistance (0.3 FTE). It started following approval of the Dutch Paediatric Society and all 932 clinically working paediatricians participate, whether personally or represented by a colleague.

Every month the Unit sends “blue cards” with ten conditions to 410 paediatricians in general hospitals, 30 cards to representatives of paediatric departments (covering 125 paediatricians) and 53 cards to contact persons for a specific disease in the eight academic hospitals (covering 397 academic paediatricians). Our child population under 15 years is about three million.

Following the report of a case, a questionnaire is sent by post from the NSCK office. Since January 2002 about 30% of the paediatricians receive an “electronic blue card”. If they report a case electronically they automatically receive a questionnaire, which they then complete and send to the investigators. The response rate in 2001 was 87% (89% for contacts in general hospitals and only 77% for contacts in academic hospitals). Where possible full case ascertainment by other sources is pursued.

To date 16 studies have been completed, ten are under surveillance and there are three studies that are under consideration.

The following studies have now been completed: sickle cell disease, thalassaemia major; postneonatal mortality in pre-dysmature children; haemolytic disease of the newborn (non ABO, non Rh D); haemorrhagic disease of the newborn; invasive *H influenzae*; congenital rubella infection; venous thromboembolic complications; hospital admissions from Rotavirus infection; group A streptococcal infection and coeliac disease.

Data for studies completed in 2001 is as follows (the number of 2001 reports is in brackets) neonatal alloimmune thrombocytopenia (30), diabetes mellitus (473), neonatal group B streptococcal disease (240), inflammatory bowel disease (82) and adrenogenital syndrome (34).

Studies currently under surveillance are: acute flaccid paralysis (30), HIV/AIDS (97), neural tube defects (72), hospital admissions pertussis (182), severe complications of medical therapy (32), atypical mycobacterial infections (25).

Studies conducted by the unit have influenced clinical practice. The surveillance unit study demonstrated that adrenogenital syndrome (AGS) screening was 100% reliable and this has now been implemented nationwide.

The study on diabetes showed that there was a strong rise in incidence, especially in children under five (this doubled in five years) and in immigrants. Further studies are urgently needed to clarify this increase.

Three studies have been approved for 2002: Idiopathic thromobocytopenia (ITP), acute ataxia, ALTE, Medium Chain Aceyl dehydrogenase deficiency (MCADD).

Coming next: influenza hospital admissions, Erb paralysis, TPN due to bowel insufficiency.

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New Zealand Paediatric Surveillance Unit (NZPSU)

The NZPSU, established in 1997, is co-directed by Professor Barry Taylor and Dr Nigel Dickson. From the beginning the NZPSU has received financial support from the New Zealand Ministry for Health to provide active surveillance of acute flaccid paralysis as part of WHO’s polio eradication initiative. Covering a child population of 0.83 million, each month over 180 paediatricians are circulated with a surveillance reply-paid card or email (depending on their preference). The mean response rate and completion rate of questionnaires has remained high at 90%.

Ten conditions are currently being surveyed. These are acute flaccid paralysis, congenital rubella, perinatal HIV exposure, haemolytic uraemic syndrome, vitamin K deficiency bleeding, subdural haemorrhage (<2 years), kawasaki disease, bronchiectasis, idiopathic nephrotic syndrome and childhood inflammatory bowel disease.

Studies on fetal alcohol syndrome, childhood diabetes (types 1 & 2) and retinopathy of prematurity (stage III) have already been completed since the NZPSU’s inception.

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Papua New Guinea Surveillance Unit

This unit began in 1996 and is closely associated with the Paediatric Association of PNG. Covering a national child population of 1.92 million there are currently 40 respondents, including all paediatricians in the country and some general physicians in the more remote areas. Response rate for the year to June 1999 was 79%. Since 1996 surveillance has been undertaken for 11 conditions. Current studies are acute flaccid paralysis (57 cases); insulin dependent diabetes mellitus (8 cases); congenital hypothyroidism (41 cases) neurologic endemic cretinism (5 cases), renal tubular acidosis (27 cases); sub-acute sclerosing panencephalitis (112 cases); necrotising enterocolitis and HIV/AIDS (64 cases). It is hoped that this year will see the commencement of nephrotic syndrome.

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Portuguese Paediatric Surveillance Unit (PPSU)

Covering a population of 1.8 million children the PPSU is the newest of the active Units established in June 2000. Surveillance commenced in March 2001 with a circulation to over 2,000 paediatric members of the Portuguese Paediatric Society. To date the response has been good with an average monthly response rate of 30%, though this is expected to rise once the database has been verified and the system become familiar to the paediatricians. Studies currently under investigation include Group B streptococcal disease, Kawasaki disease, haemolytic uraemic syndrome and insulin dependent diabetes melitus in under fives.

The PPSU had its affiliation to INoPSU approved at the second INoPSU conference and has pleasure in announcing that the PPSU will host the third conference in April 2004.

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Swiss Paediatric Surveillance Unit

The Swiss Paediatric Surveillance Unit (SPSU) was established in early 1995 under the auspices of the Swiss Paediatric Association and the Federal Office of Public Health. The German unit provided the software to run the system.

Report cards are circulated to a willing paediatrician (n=45) at each of the 38-paediatric teaching clinics representing about 250 hospital or clinic-based paediatricians (i.e. not to those delivering primary care) and covering a total child population of 1.3 million children. The response rate for the initial cards was 100% in each year, and 96-98% for the complementary questionnaires.

The eight conditions under surveillance in 2001 were: acute flaccid paralysis (15 cases), congenital rubella syndrome (0 cases), haemolytic uraemic syndrome (24 cases), tick-borne encephalitis (10 cases), varicella/zoster (83 cases) and acute rheumatic fever (6 cases), neural tube defects (38 cases), severe RSV infections (12 cases). The study on cystic periventricular leukomalacia was completed in December 1997. The study on congenital toxoplasmosis ended December 1998, with a total of 21 confirmed cases. The study on vitamin K deficiency bleeding ended in December 2000, with a total of 19 confirmed late-onset cases. In 2002 neonatal herpes simplex commenced.

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Welsh Paediatric Surveillance Unit

The Welsh Paediatric Surveillance Unit (WPSU) was set up in 1994 as a joint venture between the University of Wales Departments of Public Health Medicine (Professor S. Palmer) and Child Health (Professor J. Sibert). The management of the system was reorganised in 1996 in conjunction with the Welsh Paediatric Society, which supports the system. Funding has also been obtained

from the Welsh Office for Research and Development and latterly from the National Assembly for Wales.

The Welsh system looks at conditions considered too common for a UK study or too uncommon for a local hospital to perform. The WPSU uses the same methodology as the BPSU with whom we have a very close relationship. We discuss all our new projects with the BPSU to ensure that there is no overlap and have consequently suspended one study on subdural haemorrhages in the past.

Monthly green cards are distributed to consultant paediatricians and senior doctors of whom there are approximately 135. This covers a child population of 650,000. The overall response rate for 2001 was 89%.

When necessary, mailings can be extended to include consultant physicians and surgeons in Wales particularly where it is considered that older children may be affected. This has been very successful in studies involving acute and chronic renal failure and inflammatory bowel disease. Paediatricians along the border of England and Wales have also been very helpful where some Welsh children have been treated outside the confines of Wales.

Doctors in training may initiate studies under supervision and thereby encourage a culture of audit and research. We are not in a position to record responses by email at the moment but there are many Welsh paediatricians who are enthusiastic about such a system and this is currently being considered.

The following studies have been completed successfully: acute and chronic renal failure, severe child abuse, the critically ill child, coeliac disease, inflammatory bowel disease, children in housefires, subdural haemorrhage (I), congenital adrenal hyperplasia. Two studies were unsuccessful and were withdrawn: ingestion of household products and haemoglobinopathy. Current studies include newly diagnosed malignant disease, newly diagnosed diabetes, Marfan syndrome, childhood tuberculosis, subdural haemorrhage (II) and facial palsy.

Studies undertaken in 2002 include tuberculosis, subdural haemorrhage, septo optic dysplasia, splenectomy and hyposplenism and palliative care.

The unit hopes to provide the Welsh National Assembly with data that can assist in the planning of Health Care for Children in Wales, to act as a resource for the determination of the epidemiology of diseases in childhood and to assist audit and research.

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6 Comparison of international surveillance data: potential benefit

The Vitamin K Experience

Introduction

In the 1970s and early 1980s there were no official recommendations in Germany regarding the use of vitamin K as prophylaxis against haemorrhagic disease of the newborn. The emergence of late vitamin K deficiency bleeding (VKDB) in Germany prompted recommendations for universal intra-muscular (IM) vitamin K prophylaxis in the mid 1980's. The recommendation was based on evidence from national surveillance studies that demonstrated that late VKDB was extremely rare in children given 1-mg vitamin K IM but that one oral dose of vitamin given at birth did not confer similar protection rates (Table 5). National data from other countries confirmed these findings (1).

Following the Golding publication suggesting possible association of IM, vitamin K and childhood cancer the recommendations were changed to a three dose oral vitamin K prophylaxis regimen. A 3 times 1mg schedule proved inadequate, whereas 3 x 2mg vitamin K given orally at birth, week 2 and week 4 – 6 reduced the VKDB rate acceptably (Table 6). The rates for late VKDB, however, were still higher with oral vitamin K than with 1mg IM vitamin K prophylaxis.

Table 5: Late VKDB and vitamin K prophylaxis at birth

Country	Year	Vitamin K	Cases	Rate / 100,000	95% CI
Sweden	1991	Oral: 1-2 mg i.m. 1 mg	16 0	6 0	3.7 – 9.8 0.0 – 5.6
Switzerland	1986	Oral: 1-3 mg i.m. 1 mg	7 0	6.4 0	2.5 – 13.1 0.0 – 5.3
Japan	1992	nil Menaquinone 4 (2 mg: 1-3x)	20.4 29.5	10.5 2.8	7.0 – 15 2.0 – 3.78
UK	1991	nil Oral: 1-2 mg i.m. (1 mg)	9 7 0	4.4 1.5 0	2.0 – 8.4 0.6 – 3.2 0.0 – 0.4
Germany	1992	nil oral (1-2 mg) i.m. (s.c.) 1 mg	10 2 1	7.2 1.4 0.25	3.5 – 13.3 0.2 – 5.2 0.01 – 1.32

Table. 6: Incidence of late VKDB for different time periods in Germany

	Oral vitamin K dose	
	3 x 1 mg	3 x 2 mg
Time Period	04/93 – 12/94	01/95 – 12/98
Birth population	1,400,000	3,200,000
Number of cases	27	23
Prophylaxis failures / 100,000 live births (95% CI)		
• Complete prophylaxis	1.29 (0.24 – 0.73)	0.44 (0.76 – 2.03)
• Complete and incomplete prophylaxis	1.64 (1.04 – 2.47)	0.56 (0.33 – 0.89)

Method

Are other oral vitamin regimen more effective? Because of the rarity of late VKDB, national randomised trials are not feasible. Since different countries used different oral vitamin K regimes, comparison of VKDB bleeding rates ascertained by identical surveillance schemes using identical case definitions might be possible if each unit's study was considered as a cohort study. The "exposure" would depend on the national recommendations and "country" being a surrogate for the potential confounders. (Figure 4 below).

Results

Using this approach, the rarities of VKDB in Australia and Germany (2) were very similar when the same oral vitamin K prophylaxis was used, suggesting that such international comparison gives plausible results. The following conclusions may be drawn from these findings of national units: a) oral vitamin K may prevent late VKDB b) repeated oral doses of vitamin K are required c) the oral vitamin K regimen may be optimised by either increasing the individual doses or the number of doses d) a daily dose of 25 mg or a weekly dose of 1 mg may be as effective as 1 mg IM given at birth e) because of the extreme rarity of late VKDB, the low numbers of children exposed in the Netherlands and in Denmark preclude statistical inference regarding superiority of either of these schedules compared to the 3 times 2mg oral schedule presently used in Germany (3).

Comparison of national late VKDB rates to assess the relative effectiveness of different oral vitamin K prophylaxis regimen has to take account of the limitations listed in **Table 7**.

Conclusion

The vitamin K experience shows that comparison of national surveillance data collected in an identical manner using the same case definitions may be useful to generate hypotheses on the effectiveness of different prophylaxis regimen for very rare conditions and possibly be valid to guide public health recommendations.

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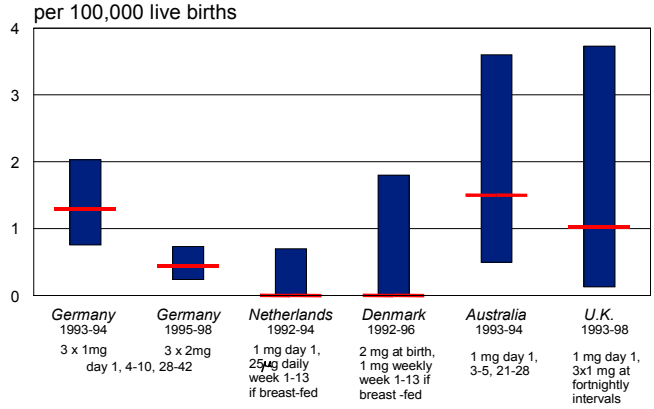
Table 7: Impact of preventive measures on the incidence of rare disorders

Prerequisites for international comparison	
• identical case definitions	• selection bias can be excluded
• constant and identical baseline incidences	• similar compliance with the preventive measure
• no differences in case ascertainment	• similar proportions of the birth cohorts are exposed to the intervention compared

Figure 5: International comparisons of rates of late VKDB related to different oral regimes



Epidemiology of HUS: an international perspective

Introduction

Haemolytic uraemic syndrome (HUS) is the most common cause of acute renal failure in children. It is characterised by microangiopathic haemolytic anaemia, thrombocytopenia and acute renal failure. HUS and thrombotic thrombocytopenic purpura (TTP) share a common pathogenesis (thrombotic microangiopathy) and are regarded as part of a disease spectrum.

Method

Six national paediatric units monitor HUS via active monthly surveillance for incident cases, with reporting by paediatricians (population > 26.5 million children <15 years; mean return rate for monthly cards 82%). Study duration ranged from 9 months (Portugal) to 7.5 years (Australia) (Table 8).

Results

A total of 786 cases were identified in six countries at the time of this analysis (Table 8)

The reported HUS rate/10^5 children < 15y varied (Australia 0.5, Britain 0.8, NZ 0.8, Canada 1.0, Switzerland 1.1). The majority of children were aged < 5 years (range 61% to 100%). Their mean age ranged from 22 months to 59 months. Overall mortality was 4% (range 0-6%). The majority (90%) of cases followed infection with Shiga toxin-producing *E.coli* and presented with diarrhoea.

Diarrhoea-associated HUS had a significant seasonal (summer) peak in all countries but NZ and Portugal where case numbers were low. Outbreaks (clusters of > 2 cases in the same region in the same time period) occurred in UK (4), Australia (1) and Canada (1). Outbreaks were associated with contaminated mettwurst, well water, meat pies and with a visit to a kindy farm. The causative organisms showed considerable heterogeneity and geographic variation. *E.coli* O157 (H7, H-, or not-typed) accounted for 96% of isolates in the UK, 94% in Canada, 38% in NZ, 13% in Switzerland and 9% in Australia. In Australia *E.coli* O111:H- predominated and caused a larger outbreak but was not seen elsewhere. All O111:H- isolates in Australia produced Shiga toxins 1 and 2 and had genes encoding for *eae* (intimin) and enterohaemolysin. A range of non-O157 isolates were reported, including O26, O55, O113, O128 and O145. *Shigella dysenteriae* was isolated in one Portuguese case and one British case.

Atypical cases (no evidence of gastrointestinal infection) had a variety of causes, most commonly infection (pnemonia, meningitis and septicaemia) with neuraminidase-producing organisms (predominantly *Strep. Pneumoniae)*. Other causes included familial HUS, STEC urinary tract infection, drugs and idiopathic.

Conclusion

INoPSU is a unique epidemiological tool which allows us to take a “snap-shot” of HUS in a variety of different settings. HUS is endemic in all countries studied and causes significant morbidity and mortality, particularly in young children. Geographic variation in the incidence, aetiology and outcome of HUS is observed. *E.coli* O157 is the most common cause of HUS in countries studied but the wide range of isolates suggests the need for rapid, reliable diagnostic tests for non-O157 serotypes. Atypical HUS has a variety of causes and with a greater likelihood or morbidity and mortality and further analysis of these data will provide new information on outcome

Elizabeth Elliott (APSU)

On behalf of Richard Lynn and Bob Adak (BPSU), Paul Sockett and Francois Proulx (CPSP), William Wong (NZ), Hans-Peter Zimmermann (Switzerland), Mario Coelho (PPSU), Diane Redmond (APSU); members of the Australian, British, Canadian, New Zealand, Swiss and Portuguese Paediatric Surveillance Units / HUS study groups.

Table 8 Data from six countries conducting surveillance of HUS

Country	Study Duration (y)	Total cases	Diarrhoea associated	Predominant Ecoli	Mortality (%)
Australia	7.5	146	124	0111:H-	5
Britain	4.0	413	395	0157:H7	2.5
Canada	1.8	123	106	0157:H7	4
New Zealand	4.0	34	29	0157:H7	6
Portugal	2	8	2	0103,055,026	0
Switzerland	4.0	70	57	Non-0157:H7	5
Total		**786**	**710(90%)**		**4**

Congenital Rubella– An international perspective: Are the results comparable?

Introduction

The risk of rubella and congenital rubella syndrome (CRS) remains forever present, as 50% of the countries around the world do not have rubella immunisation programs, while others have either incomplete, or interrupted, programs.

Using data provided by five participating paediatric surveillance units (PSUs), the rubella immunization strategies, incidence and epidemiology of CRS were compared in Australia, Canada, New Zealand, Switzerland and the United Kingdom. All PSUs used the same CRS case definition.

Results

While rubella vaccine has been universally available since the early 1970s, program strategies targeting different groups, ranging from schoolgirls to adolescents and susceptible postpartum women, have varied over the years. By the late 1980s, all of these countries included in this study had a universal first dose of rubella vaccine at between 12 and 24 months of age, and universal second dose at between 4 and 7 years by the late 1990s.

These immunisation strategies proved to be extremely successful. In the five countries included in this study, the number of reported cases of CRS decreased from a total of 69 cases in 1993 to 3 in 2001 (Table 9). In fact, four of the PSUs (Australia, Canada, New Zealand and Switzerland) have not reported any CRS cases for a year or more. However, CRS is still occurring in most countries, particularly in the immigrant population, and in women travelling, early in their pregnancy, to countries with incomplete or absent rubella immunisation programs.

- Immunisation strategies have been extremely successful in decreasing CRS incidence.
- Australia, Canada, New Zealand and Switzerland have not reported any CRS cases for one or more years.
- CRS is still occurring and is a vaccine preventable disease.

Surveillance showed evidence of missed rubella and CRS prevention opportunities, as maternal rubella immunisation was absent or unknown in more than a third (38.9%) of CRS with data. In Canada, 60% of the CRS cases had documentation of prenatal rubella susceptibility (some on previous pregnancy) and few cases represented women experiencing primary vaccine failure.

- Immunisation strategies have been extremely successful in decreasing rates of CRS
- Australia, Canada, New Zealand and Switzerland have no reported CRS for one year or more
- CRS does still occur but is vaccine preventable

Surveillance showed evidence of missed opportunities for prevention of rubella and CRS. Maternal rubella immunisation had not been given or details were unknown in more than a third (39%) of mothers of babies with CRS. In Canada, 60% of mothers of CRS cases had documented prenatal rubella susceptibility, some in the previous pregnancy. Few cases of CRS represented primary vaccine failure in the mother.

Conclusion

All five participating PSUs now have a two-dose universal rubella immunisation strategy. CRS, though rare and vaccine-preventable, still occurs. Standing orders for immunisation of rubella susceptible women in the immediate postpartum period may prevent missed opportunities for vaccination in non-immune women. Maintenance of MMR vaccine uptake at >85% is essential to decrease the risk of rubella infection and CRS.

D. Grenier, J. Doherty, A. Medaglia on behalf of all investigators and participants with the cooperation of paediatric surveillance units from Australia, Canada, New Zealand, Switzerland and the United Kingdom.

Table: 9 Congenital Rubella Syndrome Confirmed Cases

Country	Active Surveillance	Age	Jan 93-Dec 95	Jan 96-Dec 98	1999	2000	2001
Australia*	June 1993	<16 years	19	7	1	0	0
Britain	January 1990	<16 year	11	12	1	4	3
Canada†	January 1996	<1 years	N/A	3	1	1	0
New Zealand	January 1998	< 16 years	N/A	0	0	0	0
Switzerland	January 1995	< 16 years	2	1	1	0	0

* Does not include 15 CRS children not born outside Australia.

† Does not include 2 CRS children reported only to the Notifiable Diseases Reporting System (one in 1996 and one in 2000).

Progressive Intellectual & Neurological Deterioration (PIND) – The Canadian and British Perspectives

Introduction

In 1997, the BPSU commenced surveillance of PIND, with an aim to determining its incidence in the paediatric population, evaluating and classifying cases by different diagnoses, and identifying and investigating possible variant CJD (vCJD) presenting as PIND. In 1999, since Canada was both free of bovine spongiform encephalopathy and was also doing CJD surveillance, the CPSP was invited to serve as a sentinel country to the UK for PIND surveillance from July 1999 to June 2001.

Both countries used the same PIND case definition and had an expert advisory panel reviewing cases. The BPSU panel included seven paediatric neurologists, while its CPSP counterpart consisted of three paediatric neurologists, a medical geneticist and a paediatric neuropathologist.

Results

Overall, results were comparable, considering the differences in population (UK 59.5 million versus Canada 30.5 million), and duration of studies (UK five years, Canada two years).

One iatrogenic case of CJD case was reported to the CPSP. The patient underwent a duraplasty at three years of age for removal of an occipital hematoma, presented ten years later and deteriorated rapidly. Diagnosis was confirmed at autopsy. The BPSU did not have any CJD cases.

On the other hand, the BPSU received six vCJD reports – four definite and two probable – presenting similarly below 16 years of age. All had bilateral pulvinar increased signal intensity on their T2MRI and were methionine homozygous at codon 129 of the PrP gene. Autopsies confirmed the diagnoses. No vCJD cases were reported in Canada.

Interestingly, both units confirmed many different aetiologies for PIND (BPSU 90 and CPSP 20), and a similar range of conditions were documented in the two countries.

While the absence of case reports of Huntington disease and gangliosidosis to the CPSP may be due to some under-reporting, it may also be related to the successful gangliosidosis prenatal screening of the at-risk population established in the 1970s.

Both units were faced with patients – BPSU 42 and CPSP 9 – in whom no diagnosis was confirmed even after exhaustive investigations and review by the expert panel.

Conclusion

The PIND collaboration has shown that results are comparable between Canada and UK. While vCJD was reported in the UK, Canada had none. Both countries found that a variety of different difficult diagnoses presented as PIND. Even after complete investigations, the cause of PIND remains unknown in some children.

D. Grenier, J. Doherty, A. Medaglia on behalf of the study investigators Chris Verity (BPSU) and Daniel Keene (CPSP) and all participants within the British and Canadian paediatric surveillance units

Table 10 Diagnoses in children with PIND in Britain and Canada

Diagnosis	BPSU	CPSP
Neuronal ceroid lipofuscinosis	1	2
Gangliosidosis	2	*
Mucopolysaccharidosis	3	3
Mitochondrial disorders	4	1
Peroxisomal disorders	5	7
Rett syndrome	6	4
Metachromatic leukodystrophy	7	8
Niemann-Pick disease	8	6
Krabbe disease	9	5
Huntington disease	10	*

* no cases reported

Appendix 1 Published overviews on surveillance

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Appendix 2 Presentations

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Verity C. Methodology of surveillance.

Elliott E. Application of surveillance.

Stanwick R. Practicalities and differences.

King S. Mother to child transmission.

McCourt C. Perinatal surveillance.

King A. IMPACT (Immunization Monitoring Program ACTive).

Nicoll A. Ethics of surveillance.

Rosenbaum P. Surveillance in child health: Is there strength in numbers?

2nd INoPSU Conference York, United Kingdom April 2002 - Paediatric Surveillance an International Perspective

McVernon J. *Haemophilus b* vaccination strategies - is their need for a booster?

Miller E. Is there any danger associated with MMR vaccination?

Newell M-L. Reducing the risk of mother to child transmission of HIV worldwide.

Sandhu B. Is inflammatory bowel disease on the increase?

Muirhead S. Cerebral oedema and diabetic ketoacidosis.

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Appendix 3 Studies undertaken by INoPSU Members

A selection of conditions for which studies were completed by National Paediatric Surveillance Units as at January 2002 and approvals for future studies

CONDITION	UNIT PERFORMING SURVEILLANCE	
	COMPLETED STUDIES	APPROVED STUDIES
Acute Flaccid Paralysis	BPSU	
Acute Liver Failure	MPSU	
AIDS in Childhood	BPSU	
Anaphylaxis	CPSP	
Androgen Insensitivity Syndrome	BPSU	
Autoimmune Hepatitis	ESPED	
Arthrogryposis Multiplex Congenita	APSU	
Cerebral Edema in Diabetic Ketoacidosis	CPSP	
CHARGE Association		APSU, CPSP
Chemistry Set Poisoning	BPSU	
Childhood Dementia	APSU	
Children in Housefires	WPSU	
Congenital Adrenal Hyperplasia	APSU, WPSU	
Congenital Cytomegalovirus Infection		APSU
Congenital Cataracts	BPSU	
Congenital Dislocation of the Hip	BPSU	
Congenital and Neonatal Varicella	APSU	
Congenital Rubella	NSCK	
Congenital Syphilis	BPSU	
Congenital Toxoplasmosis	BPSU, SPSU	BPSU
Cystic Periventricular Leukomalacia	SPSU	
Drowning or Near-drowning	APSU, BPSU	
Extrahepatic Biliary Atresia	APSU, BPSU	
Facial Palsy	WPSU	
Fatal or Near Fatal Asthma	ESPED	
Galactosaemia	BPSU	
Group B Streptococcal Infection	CPSP	
Haemophagocytic Lymphohistiocytosis	BPSU	
Haemolytic Uraemic Syndrome	BPSU	SPSU
Haemorrhagic Disease of the Newborn (includes Vit K deficiency bleeding)	NSCK	BPSU

CONDITION	UNIT PERFORMING SURVEILLANCE	
	COMPLETED STUDIES	APPROVED STUDIES
Herpes 6/7 Virus Infection		BPSU
High Order Births	BPSU	
Haemorrhagic Shock Encephalopathy Syndrome (HSES)	BPSU, ESPED	
Idiopathic Thrombocytopenia	ESPED	
Insulin-Dependent Diabetes Mellitus	BPSU, WPSU	
Invasive *Haemophilus Influenzae i*nfection	ESPED, NSCK	APSU
Irregular Blood Group Reactions (non-D, non-ABO)	NSCK	
Juvenile Dermatomyositis	BPSU	
Kawasaki Disease	APSU, BPSU, ESPED	LPSU, MPSU
Long term Total Parenteral Nutrition	BPSU	
Lowe Syndrome	BPSU	
Marfan Syndrome	WPSU	
Medium Chain Acyl CoA Dehydrogenase Deficiency	BPSU	
MMR vaccine-associated Meningoencephilitis	BPSU	
Munchausen Syndrome by Proxy/ Non-accidental Poisoning and Suffocation	BPSU	APSU
Nephrotic Syndrome (congenital and idiopathic)		APSU
Neonatal Herpes Simplex Virus	BPSU, APSU	
Neonatal Hyperbilirubinemia		CPSP
Neonatal Thrombosis	ESPED	
Neonatal Meningitis	BPSU	
Neonatal Necrotising Enterocolitis	BPSU	
Neural Tube Defects	CPSP	
Ondine's Curse	ESPED	
Perinatal Hemocromatosis		CPSP
Physical Child Abuse	WPSU	
Post Neonatal Mortality in Premature Babies	NSCK	
Pyridoxine Dependent Status Epilepticus	BPSU	
Rett Syndrome	APSU, BPSU	Repeat study APSU
Reye's Syndrome	ESPED, BPSU	
Rheumatic Fever	BPSU, NSCK	
Rickets		CPSP
Sickle Cell Disease	NSCK	
Thalassaemia Major	NSCK, PNGPSU	
Tic borne Encephalitis	ESPED	
Transient and Permanent Neonatal Diabetes Mellitus	BPSU	
Visual Impairment and Blindness		BPSU
Water births	BPSU	
X-linked Anhydrotic Ectodermal Dysplasia	BPSU	

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