# Rare disease surveillance: An international perspective

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**BACKGROUND:** The International Network of Paediatric Surveillance Units (INoPSU) was established in 1998 and met formally for the first time in Ottawa, Ontario in June 2000.

**OBJECTIVES:** To document the methodology and activities of existing national paediatric surveillance units; the formation of INoPSU; the diseases studied by INoPSU members; and the impact of such studies on education, public health and paediatric practice.

**METHODS:** Directors of paediatric surveillance units in Australia, Britain, Canada, Germany, the Netherlands, Latvia, Malaysia, Papua New Guinea, New Zealand and Switzerland were asked to provide information on each unit's affiliations, funding and staffing; the method of case ascertainment, the mailing list and response rates; and diseases studied. Original articles that reported data derived from units were identified by a search of an electronic database (MEDLINE), and additional information was obtained from units' annual reports.

**RESULTS**: Worldwide, 10 units (established from 1986 to 1997), use active national surveillance of more than 8500 clinicians each month to identify cases of rare or uncommon diseases in a childhood population (younger than 15 years of age) of over 47 million (monthly response rate 73% to 98%). By January 1999, units had initiated 147 studies on 103 different conditions, and 63 studies were completed.

**CONCLUSION**: INoPSU enhances collaboration among units from four continents, providing a unique opportunity for simultaneous cross-sectional studies of rare diseases in populations with diverse geographical and ethnic characteristics. It facilitates the sharing of ideas regarding current methodology, ethics, the most appropriate means of evaluating units and their potential application.

**Key Words:** *International network; Paediatrics; Rare diseases; Surveillance units*

## La surveillance des maladies rares : Une perspective internationale

**HISTORIQUE :** Le Réseau international d'unités de surveillance pédiatrique (RIUSP) a été fondé en 1998 et s'est réuni officiellement pour la première fois à Ottawa, en Ontario, en juin 2000.

**OBJECTIFS :** Documenter la méthodologie et les activités des unités nationales de surveillance pédiatrique, la formation du RIUSP, les maladies étudiées par les membres du RIUSP et les répercussions de ces études sur la formation, la santé publique et l'exercice de la pédiatrie.

**MÉTHODOLOGIE :** Les directeurs des unités de surveillance pédiatrique d'Allemagne, d'Australie, du Canada, de la Lettonie, de la Malaysia, de la Nouvelle-Zélande, de la Papouasie-Nouvelle-Guinée, des Pays-Bas, du Royaume-Uni et de la Suisse ont été invités à fournir de l'information sur leur affiliation, leur mode de financement, leur personnel, leur mode d'échantillonnage de cas, leur liste d'envoi, leur taux de déclaration et les maladies à l'étude. Les articles originaux comportant des données tirées des unités ont été repérés grâce à une recherche dans une base de données électronique (MEDLINE), et des renseignements supplémentaires ont été obtenus dans les rapports annuels de chaque unité.

**RÉSULTATS :** De par le monde, dix unités ont été formées entre 1986 et 1997 et font appel à la surveillance nationale active de plus de 8 500 cliniciens tous les mois pour repérer les cas de maladies rares dans une population de plus de 47 millions d'enfants (de moins de 15 ans; taux de déclaration mensuelle de 73 % à 98 %). En janvier 1999, les unités avaient entrepris 147 études sur 103 maladies, et 63 études étaient terminées.

**CONCLUSION :** Le RIUSP favorise la collaboration entre les unités de quatre continents, ce qui fournit une occasion unique d'études croisées simultanées de maladies rares dans des populations aux caractéristiques géographiques et ethniques diverses. Il facilite le partage d'idées au sujet de la méthodologie courante, de la déontologie, des meilleurs moyens d'évaluer les unités et de l'application potentielle de la surveillance des maladies rares.

**Australian Paediatric Surveillance Unit, British Paediatric Surveillance Unit, Canadian Paediatric Surveillance Program, German Paediatric Surveillance Unit, Latvian Paediatric Surveillance Unit, Malaysian Paediatric Surveillance Unit, Papua New Guinea Paediatric Surveillance Unit, Netherlands Paediatric Surveillance Unit, New Zealand Paediatric Surveillance Unit and Swiss Paediatric Surveillance Unit*

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## BACKGROUND

### Rare disease surveillance

Rare and uncommon diseases number in the thousands, and contribute significantly to morbidity and mortality in childhood (1). Such diseases are demanding of health care resources, and have a large financial and emotional impact on families of affected children and communities. The low frequency of individual diseases may result in a delay in their recognition and diagnosis, increasing the risk of preventable complications or death. For many rare and uncommon conditions, little is known about their etiology, clinical spectrum, sequelae and management. However, to generate a sufficient number of cases to derive meaningful data, the study of rare and uncommon diseases requires data collection from large and, often, geographically diverse populations (1,2). In most countries, no mechanism has been available to enable the prospective collection of national epidemiological data on these diseases. Thus, management and resource decisions have relied on data contained in anecdotal or retrospective reports, often from a selected and potentially biased population.

In 1986, the British Paediatric Surveillance Unit (BPSU) was established to redress this deficiency (3). A joint initiative of the British Paediatric Association (now the Royal College of Paediatrics and Child Health), the Public Health Laboratory Service and the Institute of Child Health, the BPSU was based on a simple but novel concept. Each month, all paediatricians in Britain were sent a report card listing a number of rare conditions and were asked to indicate whether during that month they had seen any children who were newly diagnosed with any of the conditions listed. In 1992, Australia (2), the Netherlands (4) and Germany (5) established similar units. Malaysia followed in 1994; Switzerland (6), Canada (7), Papua New Guinea and Latvia in 1996; and New Zealand in 1997 (8). Units are currently being set up in Spain and the Republic of Ireland. In 1994 and 1998, Wales and the Republic of Ireland, respectively, established units that survey more common disorders on a regional basis. In Britain, subspecialty units conduct surveillance through the participation of gastroenterologists and opthalmologists using the methodology initially developed in Britain. The present paper represents the first collation of activities of paediatric surveillance units worldwide. MEDLINE was searched using Ovid and the terms 'paediatric surveillance' and 'surveillance unit', and additional details about publications were obtained from unit directors.

### Establishment of an International Network of Paediatric Surveillance Units

European units have met informally since 1992 to discuss research protocols and funding issues. BPSU has had close ties with the Australian Paediatric Surveillance Unit (APSU) and the Canadian Paediatric Surveillance Program. The APSU advised units in Malaysia, Papua New Guinea and New Zealand during their development. The Australian and New Zealand units have representation on each other's administrative committees, while Britain is represented on that of the Canadian unit. In 1996, units accepted the need for an International Network of Paediatric Surveillance Units (INoPSU) to formalize links among units. A proposal for INoPSU was ratified at the 22nd International Congress of Paediatrics held in Amsterdam, the Netherlands in August 1998.

The first INoPSU symposium, sponsored by Health Canada, was held in Ottawa, Canada in June 2000 in conjunction with *Beyond 2000: Healthy Tomorrows for Children and Youth,* a joint meeting of the Canadian Paediatric Society, the Canadian Institute of Child Health

**TABLE 1: Mission and aims of the International Network of Paediatric Surveillance Units**

| |
|---|
| Mission |
| The advancement of knowledge about 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 among existing units |
| the 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 International Network of Paediatric Surveillance Units Web site |
| 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 to raise awareness and encourage early diagnosis and management of rare conditions |
| identification of emerging disorders |
| establishment of international cohorts that could potentially support future research |
| development and clarification of internationally recognized diagnostic criteria |
| dissemination of new knowledge to the general public and others (eg, parent support groups) |
| prompt response to international emergencies relating to emerging rare childhood conditions |

**TABLE 2: Founding members of the International Network of Paediatric Surveillance Units**

| Founding member | Year established | Affiliations | Staffing (salaried FTE) |
|---|---|---|---|
| Australian Paediatric Surveillance Unit | 1992 | Division of Paediatrics, Royal Australasian College of Physicians<br>Centre for Disease Control, Department of Health & Aged Care | 1.8 |
| British Paediatric Surveillance Unit | 1986 | Scottish Centre for Infectious and Environmental Health<br>Faculty of Paediatrics, Royal College of Physicians (Ireland)<br>Public Health Laboratory Service<br>Royal College of Paediatrics and Child Health<br>Institute of Child Health | 1.4 |
| Canadian Paediatric Surveillance Program | 1996 | Canadian Paediatric Society<br>Centre for Infectious Disease Prevention and Control, Health Canada | 1.0 |
| 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<br>New Zealand Ministry for Health | 0.5 |
| Papua New Guinea Paediatric Surveillance Unit | 1996 | Paediatric Society for Papua New Guinea<br>HOPE worldwide (Papua New Guinea branch) | 0 |
| Swiss Paediatric Surveillance Unit | 1995 | Swiss Federation of Public Health<br>Swiss Paediatric Society | 0.3 |

*FTE Full time equivalent*

and the Canadian Academy of Child Psychiatry. INoPSU's business meeting was attended by 12 representatives from eight countries. The increasingly important issues of privacy and confidentiality of health data were discussed, and INoPSU proposed a set of ethical guidelines for surveillance programs. A symposium on *Methodological issues in paediatric surveillance* included presentations on methodology, application and practical difficulties associated with surveillance, mother-child transmission of the human immunodeficiency virus (HIV), surveillance for perinatal exposure to HIV, Canada's Immunization Monitoring Program ACTive and ethics. A keynote speaker gave the address *Surveillance in children: Is there strength in numbers?*

## Mission and aims of INoPSU

The mission of INoPSU 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". 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. Communication is enhanced by the establishment of the INoPSU Web site <http//:www.inopsu.com> that links the Web sites 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.

## INoPSU structure

Founding members of the INoPSU network are listed in Table 2. An elected secretariat oversees 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 via its Web site. BPSU acts as the INoPSU secretariat, and APSU administers INoPSU's Web site.

Most national units are affiliated with their country's professional paediatric organization, and a variety of other organizations concerned with child and public health are frequently represented on the units' administrative boards. Staffing levels vary (Table 2).

## Conditions studied and selection of studies

Paediatric surveillance units provide a mechanism for active case finding for individuals or organizations wishing to study rare or uncommon conditions in childhood. Units encourage or facilitate studies but do not generally undertake research. Units simultaneously collect monthly data on eight or more conditions. Conditions studied include infections, infection-related conditions, vaccine-preventable diseases, congenital and inherited

**TABLE 3: Conditions currently under surveillance by national paediatric surveillance units and studies that requested biological specimens at January 1999**

| Condition | Unit performing surveillance: Current 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 | |
| Chronic inflammatory bowel disease* | BPSU | |
| Celiac disease | LPSU, NSCK | LPSU |
| Congenital adrenal hyperplasia | NSCK | |
| Congenital brachial palsy | 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 in children three to 36 months of age | BPSU | BPSU |
| Fatal or near fatal asthma | MPSU | |
| Group B streptoccal infection | NSCK | |
| Hemolytic uremic syndrome | APSU, BPSU†, ESPED, NZPSU, SPSU | APSU, BPSU, NZPSU |
| Vitamin K deficiency bleeding (including hemorrhagic disease of the newborn) | APSU, CPSP, ESPED, NZPSU, SPSU | CPSP, SPSU |
| Hirschsprung disease | APSU | |
| HIV/AIDS with or without perinatal exposure to HIV | APSU, BPSU, LPSU, MPSU, NSCK, NZPSU, PNGPSU | BPSU, LPSU |
| Hospitalized pertussis | ESPED, NSCK | |
| Idiopathic thrombocytopenia | ESPED | |
| Insulin-dependent diabetes mellitus | ESPED, LPSU, NSCK, PNGPSU, NZPSU | LPSU |
| Invasive *Haemophilus influenzae* infection | APSU, BPSU, ESPED | APSU, BPSU |
| Ischemic stroke in infants | ESPED | |
| Leukemia | LPSU | LPSU |
| Lues congenita | LPSU | LPSU |
| Multiple sclerosis in infants | ESPED | |
| Neonatal fungal septicemia | ESPED | |
| Neonatal herpes simplex virus infection | APSU, NZPSU | |
| Neonatal meningitis | MPSU | |
| Neural tube defects | NSCK | |
| Neurological endemic cretinism | PNGPSU | |
| Organocidopathia and fatty acid oxidation defects | ESPED | |
| Paediatric malignancies‡ | PNGPSU | |
| Pneumoccoccal sepsis and/or meningitis | ESPED | ESPED |
| Prader-Willi syndrome | APSU | |
| Primary immunodeficiency disorders§ | APSU | |
| Progredient subacute neurological diseases | LPSU | LPSU |
| Progressive intellectual and neurological deterioration (including Creutzfeld-Jakob disease) | BPSU, CPSP | CPSP |
| Renal tubular acidosis | PNGPSU | |
| Retinopathy of prematurity (stage III and beyond) | NZPSU | |
| Reye syndrome | BPSU | |
| Rotavirus infection | NSCK | |
| Severe combined immunodeficiency | APSU | |
| Subacute sclerosing panencephalitis | APSU, BPSU, CPSP, PNGPSU | CPSP, PNGPSU |
| Subdural hematoma or effusion (in children younger than two years of age) | BPSU, NZPSU | |
| Transient myeloproliferative syndrome in newborns with Down syndrome | ESPED | |
| Venous thromboembolic complaints | NSCK | |

**Ulcerative colitis, Crohn's disease and intermediate colitis; †Previously studied by the British Paediatric Surveillance Unit (BPSU) from 1986 to 1989; ‡Wilms tumour, Burkitt lymphoma, leukemia, neuroblastoma, lymphoma (non-Burkitt), other; §Predominantly antibody defects (eg, X-linked agammaglobulinemia, immunogloblulin A deficiency, immunogloblulin G 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 edema), defects of phagocytic function (eg, chronic granulomatous disease, leukocyte-adhesion deficiency, Schwachman syndrome) and other. AIDS Acquired immunodeficiency syndrome; APSU Australian Paediatric Surveillance Unit; CPSP Canadian Paediatric Surveillance Program; ESPED Erhebungseinheit fur Seltene Padiatrische Erkrankungen in Deutschland; HIV Human immunodeficiency virus; LPSU Latvian Paediatric Surveillance Unit; MPSU Malaysian Paediatric Surveillance Unit; NSCK Nederlands Signalerings-Centrum Kindergeneeskunde; NZPSU New Zealand Paediatric Surveillance Unit; PNGPSU Papua New Guinea Paediatric Surveillance Unit; SPSU Swiss Paediatric Surveillance Unit*

diseases, unusual injuries or therapies, and rare complications of common diseases. Current and completed studies and conditions approved for future study are shown in Tables 3 and 4; they indicate a considerable overlap among units. By the start of 1999, the 10 units had initiated 147 studies on 103 different conditions. At this time, 63 of these studies had been completed and a further 12 applications had been approved for new studies. Eight collaborative studies have been undertaken among units. Some studies also incorporate the collection of biological specimens from notified cases (Table 3).

Applications to conduct a study are considered by a scientific panel with epidemiological and public health expertise, and may also be reviewed externally by experts in the field. To be approved for study, conditions must fulfill certain criteria. They must be sufficiently uncommon so that they do not overload the system, although short-duration studies of relatively common conditions may be studied. Research questions must be important and, ideally, all patients should be seen by clinicians whose names are on the mailing list. Similar data should not be readily available through an existing source, although when alternative sources are available, their use is encouraged, particularly when the study aims require complete or near complete case ascertainment. Studies must conform to international ethical guidelines (*International Ethical Guidelines for Biomedical Research Involving Human Subjects* [9] prepared by the Council for International Organizations of Medical Sciences and the World Health Organization in 1993).

Studies judged to be feasible and to have sufficient resources are monitored for one to three years initially. Studies may be extended if the condition is of particular public health significance (eg, HIV and AIDS) or the paediatric surveillance unit is the optimal mechanism for gathering routine surveillance data. A protocol sheet outlining study aims, case definition and reporting instructions is distributed to the mailing list before the commencement of a new study.

## METHODS

### Data collection

According to the principle of 'active' surveillance, initiation for notification comes from the unit rather than the clinician. Active surveillance results in considerably higher case ascertainment than passive surveillance, and minimizes recall bias (2). The methodology varies slightly among units to suit local conditions. In principle, the surveillance unit sends a monthly report card to a 'mailing list' of paediatricians and asks paediatricians simply to indicate whether they have 'nothing to report', or to mark the number of new cases of each condition listed that they saw during the previous month. Cards are returned to the unit. The individual or organization responsible for a study (the 'investigator') is notified about positive case reports and given the contact details for the reporting clinician. The investigator is then responsible for obtaining clinical and epidemiological data from reporting doctors by postal questionnaire, and for the collation, analysis, presentation and publication of data and feedback to the unit's secretariat. Alternative data sources may be used to validate ascertainment. In most countries, data collection is anonymous; investigators use a patient code and have no direct access to information that would allow them to identify or contact patients, or their families (Table 5).

Some units use a reply-paid report card, and e-mail reporting was introduced in Australia in 1997 (Table 5). Telephone and facsimile reporting is requested for some studies when a timely report is required (eg, to facilitate obtaining biological specimens). On receipt of a case notification, two units (the Canadian Paediatric Surveillance Program and the New Zealand Paediatric Surveillance Unit) send study questionnaires directly to the notifying clinician rather than sending the notifying doctor's details to the investigator in an attempt to make the receipt of questionnaires more timely (8). In 1998, the return rate of monthly cards to units ranged from 73% to 98%, and that of questionnaires ranged from 47% to 100% (Table 5). The proportion of clinicians who report by e-mail to APSU increased from 14% in 1997 to over 30% in 1999, with a 99% response rate (Table 5). The workload for most clinicians who participate in national surveillance of rare diseases is low. In any single year, a large proportion of clinicians on mailing lists do not report a single case and, hence, are not required to complete a questionnaire requesting further details (10,11).

### Mailing lists

In 1998, mailing lists ranged in size from seven to 2125 individuals (Table 6), and included general and specialist paediatricians and nonpaediatric specialists (eg, paediatric surgeons and dermatologists). In Switzerland, Germany and Latvia, department heads rather than individual clinicians report on behalf of their colleagues. Surveillance covers the national population younger than 15 years of age, which ranges from 0.5 million individuals in Latvia to approximately 13 million patients in the British Isles (Table 6). Currently, over 8500 paediatricians worldwide contribute monthly to the reporting of uncommon diseases in a population of over 47.6 million.

### Funding sources

Units represent 'value for money' because they conduct up to 15 research studies simultaneously; however, fixed costs 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 a major funder in Australia and Canada. In some countries, an investigator fee contributes towards infrastructure costs and ranges from EURO€111 to EURO€5555 per year.

**TABLE 4: Conditions for which studies were completed by national paediatric surveillance units at January 1999, 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 |
| Chemistry set poisoning | BPSU | |
| Childhood dementia | APSU | |
| Congenital adrenal hyperplasia | APSU | |
| 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 | |
| Cystic periventricular leukomalacia | SPSU | |
| Drowning or near-drowning | APSU, BPSU | |
| Extrahepatic biliary atresia | APSU, BPSU | |
| Fatal or near fatal asthma | ESPED | |
| Galactosemia | BPSU | |
| Group B streptoccal infection | CPSP | |
| Hemophagocytic lymphohistiocytosis | BPSU | |
| Hemolytic uremic syndrome | BPSU (study recommenced in 1997) | SPSU |
| Hemorrhagic disease of the newborn (includes vitamin K deficiency bleeding) | NSCK | BPSU |
| Herpes 6/7 virus infection | | BPSU |
| High order births | BPSU | |
| Hemorrhagic shock encephalopathy syndrome | BPSU, ESPED | |
| Idiopathic interstitial lung disease | | CPSP |
| Idiopathic thrombocytopenia | ESPED | |
| Insulin-dependent diabetes mellitus | BPSU | |
| Invasive *Haemophilus influenzae* infection | 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 | |
| Medium chain acyl CoA dehydrogenase deficiency | BPSU | |
| Measles-mumps-rubella vaccine-associated meningoencephilitis | BPSU | |
| Munchausen syndrome by proxy and/or nonaccidental poisoning and suffocation | BPSU | APSU |
| Nephrotic syndrome (congenital and idiopathic) | | APSU |
| Neonatal thrombosis | ESPED | |
| Neonatal meningitis | BPSU | |
| Neonatal necrotising enterocolitis | BPSU | |
| Neural tube defects | CPSP | |
| Ondine's curse | ESPED | |
| Perinatal hemocromatosis | | CPSP |
| Postneonatal mortality in premature babies | NSCK | |
| Pyridoxine-dependent status epilepticus | BPSU | CPSP |
| Rett syndrome | APSU, BPSU | Repeat study APSU |

*Continued on next page*

**TABLE 4: Conditions for which studies were completed by national paediatric surveillance units at January 1999, and approvals for future studies (continued)**

| | | |
|---|---|---|
| Reye syndrome | ESPED | |
| Rheumatic fever | BPSU, NSCK | |
| Rickets | | CPSP |
| Sickle cell disease | NSCK | |
| Thalassemia 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 | |

*AIDS Acquired immunodeficiency syndrome; APSU Australian Paediatric Surveillance Unit; BPSU British Paediatric Surveillance Unit; CHARGE Coloboma, heart defects, atresia choanae, retardation of growth and development and/or central nervous system anomalies, genital anomalies and/or hypogonadism, and ear anomalies and/or hearing loss; CPSP Canadian Paediatric Surveillance Program; ESPED Erhebungseinheit fur Seltene Padiatrische Erkrankungen in Deutschland; LPSU Latvian Paediatric Surveillance Unit; MPSU Malaysian Paediatric Surveillance Unit; NSCK Nederlands Signalerings-Centrum Kindergeneeskunde; NZPSU New Zealand Paediatric Surveillance Unit; PNGPSU Papua New Guinea Paediatric Surveillance Unit; SPSU Swiss Paediatric Surveillance Unit*

**TABLE 5: Reporting mechanisms used by member countries of the International Network of Paediatric Surveillance Units**

| Country | Reply-paid cards | Report cards (% returned) | Other forms of reporting (conditions reported) | Questionnaire (% returned) |
|---|---|---|---|---|
| Australia | Yes | 93 | Telephone (AFP)<br>E-mail (all conditions) | 66 to 97 |
| Britain | No | 94 | Telephone (AFP, IILH, Hib, HUS, encephalitis) | 85 to 98 |
| Canada | Yes | 86 | None | 90 to 100 |
| Germany | No | 95 | None | 47 to 100 |
| Latvia | No | Not known | Telephone (all conditions)<br>E-mail (all conditions) | Not known |
| Malaysia | Yes | 75 | None | Not known |
| Netherlands | Yes | 92 | Telephone (Pertussis) | 93 |
| New Zealand | Yes | 94 | Telephone (AFP, HUS)<br>Fax (AFP, HUS)<br>E-mail (AFP/HUS) | Not known |
| Papua New Guinea | Yes | 72.7 | None | Not known |
| Switzerland | Yes | 98 | None | 96 to 100 |

**129 (14%) of 928 clinicians reported to the Australian Paediatric Surveillance Unit by e-mail in 1998, and over 30% used e-mail reporting in 1999. AFP Acute flaccid paralysis; IILH Idiopathic interstitial lung disease; Hib* Haemophilus influenzae *type b; HUS Hemolytic uremic syndrome*

## RESULTS

### Evaluation

The Australian unit has undergone formal evaluation (12), and some of its findings are applicable to other units. The evaluation 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. The sensitivity of case ascertainment was acceptable for most APSU studies, and the positive predictive value was over 70% for most notifications.

Although desirable, full case ascertainment is not always achieved (1,12-14). Indeed, complete case ascertainment is not always required to fulfill the aims of some studies, especially when the system aims to identify cohorts that are later invited to enter randomized control trials or clinical surveys. However, it is important that

**TABLE 6: Mailing lists used by member countries of the International Network of Paediatric Surveillance Units**

| Country | Population younger than 15 years of age (millions) | Number of clinicians on mailing list |
|---|---|---|
| Australia | 2 | 928 |
| Britain | 12.8 | 1925 |
| Canada | 6 | 2125 |
| Germany | 12 | 496* |
| Latvia | 0.5 | 7* |
| Malaysia | 7.6 | 340 |
| Netherlands | 2.8 | 416 |
| New Zealand | 0.8 | 163 |
| Papua New Guinea | 1.8 | 40 |
| Switzerland | 1.3 | 41† |

**Reporting by heads of hospital paediatric units; †Reporting by heads of paediatric centres on behalf of 500 respondents*

mailing lists are as inclusive (hence as representative) as possible, to maximize ascertainment. A comparison of the BPSU mailing list with the 1996 national paediatric manpower census identified the involvement of 96% of all paediatricians who are most likely to see cases (15). Where full ascertainment is desired, alternative sources of data are used to supplement surveillance unit data. These sources include birth defect registers, death registers, parent support groups and laboratory surveillance programs (1,16). When used in conjunction with other data sources, this methodology results in levels of case ascertainment between 70% and 95% (15,17-19).

The APSU evaluation concluded that the support of professional paediatric bodies, the simplicity of the reporting scheme, the low workload for clinicians, and the educational value and relevance for clinical practice accounted for the high compliance within these schemes (12).

## Impact

The effectiveness of units is measured by their impact on education and public health. Educational impact is achieved by the dissemination of information via newsletters, annual reports, presentations to scientific meetings and publication in the scientific literature. In the APSU evaluation, the majority of clinicians reported that the provision of diagnostic criteria and information derived from studies was educationally useful, and 33% of respondents reported said that such information had informed or changed their clinical practice (12). The increase in reports of Kawasaki disease in the British Isles during 1986/87 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 (20). A similar phenomenon occurred in Australia when congenital and neonatal varicella became notifiable to the APSU (21).

Many units have affected public health by monitoring outcomes of national vaccination programs, the late sequelae of vaccination or the incidence of vaccine-preventable conditions before the availability of vaccination. These monitoring effects include surveys of congenital rubella (21,22), subacute sclerosing panencephalitis (23), meningoencephalitis after measles-mumps-rubella vaccination (24), acute flaccid paralysis (25,26) and *Haemophilus influenzae* type b vaccine failures (14,27), with the latter being a part of a collaborative Dutch and 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 (28-33). Other units are monitoring the association between hemolytic uremic syndrome and Shiga toxin-producing *Escherichia coli* (34,35). The recent identification of new variant Creutzfeld-Jakob disease in Britain (36) has led to the monitoring of the incidence and etiology of progressive intellectual and neurological degeneration in childhood (37). Studies have also provided information that has influenced public health policy development as follows.

- Studies of HIV/AIDS and perinatal exposure to HIV provided information on perinatal transmission of HIV (38), and the role of screening and treatment in pregnancy (17,39).
- Studies on toxoplasmosis and neonatal herpes simplex virus infection concluded that universal screening in pregnancy was not warranted due to insufficient case frequency (40,41).
- Repeated warnings about the danger of using acetylsalicylic acid in childhood were issued after the BPSU study on Reye syndrome described the continued association between acetylsalicylic acid use in children and this disorder (42,43).
- The APSU study on hemolytic uremic syndrome provided data to the National Food Authority to support a change in the Food Standards Code relating to the safety of fermented meat small goods products (34,44).
- Studies allowed the evaluation of prevention strategies such as pool fencing (45).
- Studies identified potential risk factors, for example epilepsy for drowning (45), or being the child of an immigrant parent not vaccinated for congenital rubella (46).
- The BPSU study on chemistry set poisoning supported data that led to changes in European Union law regarding the packaging of children's toys (47).

Some studies, for example, on Rett Syndrome (48-50), provided insight into disease etiology and identified cohorts for future research, including randomized clinical trials of treatment (51). Studies also provided information on current management strategies, such as the use of immunoglobulin in Kawasaki disease (20,52), and the usefulness of a pilot neonatal screening program for congenital adrenal hyperplasia (53). Data from studies also allowed the validation of diagnostic criteria (52), documentation of short term outcomes (26,45) and the description of the clinical spectrum of disease (54). Dutch, British and German units collaborated on surveillance of insulin-dependent diabetes mellitus in children younger than five years of age (18), while Dutch and British units collaborated on a study on *H influenzae* type b vaccine failures (27). The use of several Australian study protocols (hemolytic uremic syndrome, congenital rubella, acute flaccid paralysis, HIV/AIDS, neonatal herpes simplex virus infection and vitamin K deficiency bleeding) by New Zealand researchers will allow international comparison of data. The exciting potential for the simultaneous study of a single condition by all INoPSU member countries also exists.

## CONCLUSIONS

In formalizing established links among 10 existing national paediatric surveillance units, INoPSU provides a unique mechanism for the development of international collaborations. INoPSU allows the collection of information from member nations with diverse geographical locations and population characteristics, the development of uniform diagnostic criteria and the dissemination of new knowledge that will benefit paediatric care. A crucial role of INoPSU will be to ensure the ongoing evaluation of the methodology used by units and the quality of data collected.

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