



# REPORT

## CANADIAN PAEDIATRIC SURVEILLANCE PROGRAM

**2004  
RESULTS**



## **Mission Statement**

*To contribute to the improvement of the health of children and youth in Canada by national surveillance and research into childhood disorders that are high in disability, morbidity, mortality and economic costs to society, despite their low frequency.*

**For more information on the  
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# Acknowledgements

The key strength of the Canadian Paediatric Surveillance Program (CPSP) is its commitment to the improvement of the health of children and youth in Canada and around the world. This would not be possible without the participation of Canadian paediatricians, subspecialists and other health-care providers in the monthly collection of information on rare paediatric conditions, our principal investigators who review and analyze the data to provide knowledge and educational solutions, and the guidance of our Steering Committee members. We thank them all.

For their role in the verification of data collected, we thank:

- Canadian Association of Paediatric Health Centres
- Canadian Institute for Health Information
- Canadian Paediatric Decision Support Network
- IMPACT (Immunization Monitoring Program ACTive) centres
- Notifiable Diseases Reporting System, Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada

We also gratefully acknowledge the financial support received to maintain and expand the program. A summary of supporters is found in this report (page 8).

The strong partnership between the Canadian Paediatric Society (CPS) and the Public Health Agency of Canada (PHAC) allows the CPSP to grow in Canada and to take a leadership role on the international scene.

## A special thank you

Dr. Susan King is a leader in paediatric surveillance. A very active and valued member of the CPS Infectious Diseases and Immunization Committee and the CPSP Steering Committee, Dr. King has always provided excellent infectious disease expertise and has been greatly appreciated for her astuteness and insight when reviewing study proposals.

As a coordinator of the Canadian Perinatal HIV Surveillance Program, a major accomplishment was ensuring that epidemiological research information confirming the effectiveness of early intervention was actually integrated into public health practice with affected groups.

Her strong commitment to and experience in collecting accurate clinical information, while scrupulously respecting individual privacy and professional confidentiality, are tremendous contributions not only to the CPSP but to all children and youth with uncommon high-impact conditions.

Through her vision and actions, Dr. Susan King created a world where the meaning of “caring” is truly expressed.

What an inviting path. What a lady!



Dr. Susan King  
*“CPSP’s greatest strength  
 is collecting national data  
 in a timely manner.”*

# Foreword

## Federal Minister of Health

As Minister of Health, I would like to congratulate and thank the Canadian Paediatric Society (CPS) for the successful completion of the 2004 Canadian Paediatric Surveillance Program (CPSP). The coordination of the surveillance activities by the CPS, and the contributions from the network of more than 2,400 paediatricians, make this program a success.

The CPSP is a valuable tool for the surveillance of rare childhood conditions. The knowledge generated through the program facilitates research and advances awareness and education within the medical profession, improving the quality of care of children with rare conditions.

The Government of Canada is working with partners in the provinces and territories to renew our health-care system and ensure that all Canadians have access to quality care. The knowledge and commitment of paediatricians across Canada, and the contributions from professional organizations like the CPS, will continue to play a key role in the attainment of these objectives.

Congratulations and thank you for your continued efforts.



The Honourable Ujjal Dosanjh

## Chief Public Health Officer of Canada

I am pleased to accept the ninth annual report of the Canadian Paediatric Surveillance Program (CPSP), an important collaborative tool for surveillance, research and policy development.

It is especially commendable that the epidemiological data generated through the program is used as a catalyst for providing information to physicians to raise awareness and improve treatment of rare diseases and conditions affecting children.

That is why I am pleased that the Public Health Agency of Canada, through the Centre for Infectious Disease Prevention and Control (CIDPC), partners with the Canadian Paediatric Society on this initiative. The Agency was established in September 2004 to serve as the focal point for research and expertise on public health issues, including disease surveillance, by working closely with provinces and territories and other stakeholders to improve the overall health of Canadians.

I would like to personally thank the Agency's staff who have contributed to the success of this program by serving as principal investigators, program managers and/or members of the CPSP Steering Committee. Agency and Health Canada studies in 2004 include acute flaccid paralysis, congenital rubella syndrome, adverse drug reactions (serious and life-threatening), early-onset eating disorders, severe combined immunodeficiency and a one-time survey on injuries associated with infant bath seats.

The program would not be the success that it is without the support of the paediatricians across Canada who provide the surveillance data by completing detailed reports on each case.

I look forward to being informed of new knowledge generated by the surveillance program.



Dr. David Butler-Jones

## President of the Canadian Paediatric Society

The Canadian Paediatric Society is very proud of the success of the CPSP. From its inception in 1996, the program has become well established and respected within both the paediatric and public health communities. As an active participant in the CPSP, I am impressed by its scope and versatility and, above all, by the impact it has had on health practice and policy.

As a neonatologist, I have been especially interested in study results that have reinforced the judicious public health decision for a two-dose rubella vaccine regimen that has resulted in zero to two cases of congenital rubella syndrome per year; and the polio strategy with no polio-related acute flaccid paralysis reported. Furthermore, as CPS President, I was heartened by findings that reaffirm the importance of CPS recommendations for vitamin D supplementation of all exclusively breast-fed infants in order to prevent nutritional rickets, and adequate assessment and follow-up of early-discharged infants with hyperbilirubinemia in preventing kernicterus.

Recognition of the CPSP extends far beyond Canada. This year, the CPSP worked with the International Network of Paediatric Surveillance Units, the International Paediatric Association and the Argentinian Paediatric Society.

The Public Health Agency of Canada merits special thanks and deserves credit for envisioning the potential of pan-Canadian collaborative epidemiological paediatric surveillance.

Finally, I would like to thank my colleagues who diligently complete and return the check-off form each month. They deserve a round of applause for contributing to the success of the program.



Dr. C. Robin Walker

## CPSP Chairman

Once again, a great year!

After a successful program evaluation in 2003, the CPSP entered its ninth year of pan-Canadian surveillance with an all-time high of 13 simultaneous studies.

CPSP surveillance data is most meaningful when it invokes action in the form of public health policy and standards of practice. This year, two examples illustrate what I would call '*Surveillance results into action*'.

- Canadian incidence data on injuries associated with baby walkers provided evidence to support Health Canada's legislative ban on baby walkers announced in April 2004.
- The National Advisory Committee on Immunization revised its statement on varicella vaccine. Data from the CPSP study on necrotizing fasciitis (NF), which reinforced the relation between chickenpox and NF, supported the need for a universal varicella immunization program and demonstrated the severity of infection with children experiencing surgical interventions and prolonged hospitalizations.



Dr. Gilles Delage

The CPSP, through its membership in the International Network of Paediatric Surveillance Units (INoPSU), fosters international collaboration and cooperation between investigators and encourages simultaneous research for the benefit of children who live in the 'global village'. Eight of the 13 current studies and three of the four accepted new studies are also being undertaken by at least one other national surveillance unit in INoPSU.

Documenting the health status of the paediatric population is an obligation and the CPSP is committed to doing this through surveillance, education and advocacy. I encourage you to read this report to better understand the pertinence of study results to your practice.

## CPSP Steering Committee

Dr. Gilles Delage (Chair)	Canadian Paediatric Society
Dr. Garth Bruce	Canadian Paediatric Society
Dr. Rick Cooper	Paediatric Chairs of Canada
Ms. Marie Adèle Davis	Canadian Paediatric Society
Ms. Jo-Anne Doherty	Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada
Dr. Danielle Grenier	Canadian Paediatric Society
Dr. Richard Haber	Canadian Paediatric Society
Dr. Susan King	Canadian Paediatric Society
Dr. Simon Levin	Canadian Association of Child Neurology
Dr. Catherine McCourt	Centre for Healthy Human Development, Public Health Agency of Canada
Ms. Andrea Medaglia	Canadian Paediatric Society
Mr. Paul Muirhead	Consultant
Dr. Jeff Scott	Council of Chief Medical Officers of Health
Ms. Sarah Srikanthan	Canadian Paediatric Society
Dr. Anne Summers	Canadian College of Medical Geneticists
Dr. Paul Varughese	Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada
Dr. Wendy Vaudry	IMPACT (Immunization Monitoring Program ACTive)
Dr. Lynne Warda	Canadian Paediatric Society
Dr. Lonnie Zwaigenbaum	Canadian Paediatric Society

## CPSP Working Group

Ms. Andrea Medaglia (Chair)	Canadian Paediatric Society
Ms. Sarah Srikanthan (Co-Chair)	Canadian Paediatric Society
Ms. Marie Adèle Davis	Canadian Paediatric Society
Ms. Jo-Anne Doherty	Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada
Dr. Danielle Grenier	Canadian Paediatric Society



A fond farewell to Andrea Medaglia, Senior Coordinator, who retired in December 2004 after nine years of dedicated service. Her sense of organization greatly contributed to the success of the CPSP. Our many thanks and best wishes in her future projects.

# Publications in 2004

## Published papers related to studies

(See [www.cps.ca/english/cpsp](http://www.cps.ca/english/cpsp) for a complete list of abstracts with hotlinks.)

Neonatal herpes simplex virus infections in Canada. Kropp RY, Wong T, Burton S, Embree J, Steben M. *Int J STD AIDS: Clin Pract Sex Health* 2004;15(S1):2

Incidence of Smith-Lemli-Opitz syndrome in Canada: Results of three-year population surveillance. Nowaczyk MJM, Wayne JS, Zeesman S, Douketis JD. *J Pediatr* 2004;145(4):530-5

Canadian Paediatric Surveillance Program evaluation: An excellent report card. Grenier D, Doherty J, MacDonald D, Scott J, Delage G, Medaglia A, Davis MA. *Paediatr Child Health* 2004;9(6):379-384

Surveillance for progressive intellectual and neurological deterioration in the Canadian paediatric population. Keene DL, Sutcliffe T, Harman P, Grenier D. *Can J Neurol Sci* 2004;31(2):220-4

Canadian Paediatric Surveillance Program confirms low incidence of haemorrhagic disease of the newborn in Canada. McMillan DD, Grenier D, Medaglia A. *Paediatr Child Health* 2004;9(4):235-8

Canadian Paediatric Surveillance Program: A developmental check-up. Scott J. *Paediatr Child Health* 2004;9(1):13-4

## Highlights published in *Paediatrics & Child Health*

(See [www.cps.ca/english/cpsp](http://www.cps.ca/english/cpsp) for a complete list of highlights with hotlinks.)

Canadian Paediatric Surveillance Program 2004 quiz. *Paediatr Child Health* 2004;9(10):718,748

Are acquired demyelinating syndromes of the central nervous system underdiagnosed in Canadian children? *Paediatr Child Health* 2004;9(9):638

Rights to individual privacy and professional confidentiality – A Canadian Paediatric Surveillance Program ongoing commitment. *Paediatr Child Health* 2004;9(8):535

The challenge of jaundiced newborns – Unravelling the etiology. *Paediatr Child Health* 2004;9(7):511

CPSP contributes to research: Call for new studies. *Paediatr Child Health* 2004;9(6):372

CPSP evaluation: A process based on WHO and CDC guidelines. *Paediatr Child Health* 2004;9(5):322

What does the CPSP have to do with public health? *Paediatr Child Health* 2004;9(3):155

The multiple facets of bone diseases. *Paediatr Child Health* 2004;9(2):80

# Presentations in 2004

(See [www.cps.ca/english/cpsp](http://www.cps.ca/english/cpsp) for a complete list of presentations with hotlinks.)

## National

Documenting polio eradication: the role of stool investigation in Canada. Jain S, Macey J, Varughese P, Tam T, King A. Presented at the 6<sup>th</sup> Canadian Immunization Conference, Montreal, December 5-8, 2004.

Public health impact of necrotizing fasciitis and neonatal herpes simplex virus infection. Grenier D, Medaglia A. Presented at the 6<sup>th</sup> Canadian Immunization Conference, Montreal, December 5-8, 2004.

Public health impact of the Canadian Paediatric Surveillance Program (CPSP). Grenier D, Doherty J,

Medaglia A. Presented at the 2004 Annual Meeting of the Canadian Association of Paediatric Health Centres, Montreal, November 7-10, 2004.

Severe neonatal hyperbilirubinemia in Canadian newborns: A preventable disease? Campbell D. Presented at the 2004 Annual Meeting of the Canadian Association of Paediatric Health Centres, Montreal, November 7-10, 2004.

Public health impact of the Canadian Paediatric Surveillance Program (CPSP). Davis MA. Presented at the 137<sup>th</sup> Annual Meeting of the Canadian Medical Association, Toronto, August 15-18, 2004.

The changing face of bone diseases. Scriver C. Presented at the 81<sup>st</sup> Annual Meeting of the Canadian Paediatric Society, Montreal, June 17, 2004.

The many faces of osteogenesis imperfecta. Glorieux F. Presented at the 81<sup>st</sup> Annual Meeting of the Canadian Paediatric Society, Montreal, June 17, 2004.

Vitamin D deficiency in rickets (VDDR) among children living in Canada: A new look at an old disease. Ward LM. Presented at the 81<sup>st</sup> Annual Meeting of the Canadian Paediatric Society, Montreal, June 17, 2004.

Severe neonatal hyperbilirubinemia: Cause for concern? Campbell DM, Sgro M, Shah V. Presented at the 81<sup>st</sup> Annual Meeting of the Canadian Paediatric Society, Montreal, June 16-20, 2004.

Evaluation of the Canadian Paediatric Surveillance Program – Process and results. Grenier D, Medaglia A, Doherty J. Presented at the 81<sup>st</sup> Annual Meeting of the Canadian Paediatric Society, Montreal, June 16-20, 2004.

Public health impact of the Canadian Paediatric Surveillance Program (CPSP). Grenier D, Doherty J, Medaglia A. Presented at the 81<sup>st</sup> Annual Meeting of the Canadian Paediatric Society, Montreal, June 16-20, 2004.

Canadian Paediatric Surveillance Program (CPSP) public health outcomes. Doherty J. Presented at the 95<sup>th</sup> Annual Conference of the Canadian Public Health Association, St. John's, June 13-16, 2004.

Subacute sclerosing panencephalitis: A report on the Canadian Paediatric Surveillance Program. Levin S, Campbell C, Humphreys P, Brannan R, Walop W. Presented at the 39<sup>th</sup> meeting of the Canadian Congress of Neurological Sciences, Calgary, June 8-12, 2004.

## International

International Network of Paediatric Surveillance Units (INoPSU). Elliott E, Grenier D, Medaglia A. Presented at the 24<sup>th</sup> International Congress of Pediatrics, Cancun, August 17, 2004.

Seminario Sobre Vigilancia Epidemiologica Neonatal: La Experiencia de la Sociedad Canadiense de Pediatria. Grenier D, Medaglia A. Presented at Hospital Fernandez, Buenos Aires, July 21-22, 2004.

Prospective national Canadian paediatric surveillance program for necrotizing fasciitis. Davies HD. Presented at the Pediatric Academic Societies' Annual Meeting, San Francisco, May 2, 2004.

Outcome of group A streptococcal (GAS) necrotizing fasciitis: Evidence from a Canadian national study. Davies HD. Abstract published for Pediatric Academic Societies' Annual Meeting, San Francisco, May 1-4, 2004.

Neonatal herpes simplex virus infections in Canada. Kropp RY, Wong T, Burton S, Embree J, Steben M. Presented at the BASHH/ASTDA Spring Meeting, Bath, May 2004.

Beyond counting numbers documenting public health impacts of paediatric surveillance. Grenier D. Presented at the 3<sup>rd</sup> Conference of the International Network of Paediatric Surveillance Units (INoPSU), Lisbon, April 21-24, 2004.

Second data sources and their validity. Grenier D. Presented at the 3<sup>rd</sup> Conference of the International Network of Paediatric Surveillance Units (INoPSU), Lisbon, April 21-24, 2004.

Public health impact of the Canadian Paediatric Surveillance Program. Doherty J. Presented at the 3<sup>rd</sup> Conference of the International Network of Paediatric Surveillance Units (INoPSU), Lisbon, April 21-24, 2004.

Rare diseases research through surveillance: The Canadian experience. Medaglia A. Presented at the 3<sup>rd</sup> Conference of the International Network of Paediatric Surveillance Units (INoPSU), Lisbon, April 21-24, 2004.

Congenitally deafblind persons with CHARGE association. Blake K. Presented at the Nordic Staff Training Centre for Deafblind Services (four-day workshop). Dronninglund Castle, January 2004.

CHARGE into the adolescent and adult decades – videoconference. Blake K. Presented at the Nordic Staff Training Centre for Deafblind Services (four-day workshop). Dronninglund Castle, January 2004.

## Funding

To date, funding for the surveillance program has been made available from the Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada, as well as other government departments, organizations and companies interested in increased knowledge of uncommon childhood conditions and the practical improvement in prevention and treatment.

Funding is required for program management including administrative and financial support. Educational grants are welcome from all interested in monitoring and contributing to the improvement of health of Canadian children and youth.

We gratefully acknowledge funding from the following sources:

### Government departments

#### Health Canada

- First Nations and Inuit Health Branch
  - Office of Community Medicine
- Health Products and Food Branch
  - Marketed Health Products Directorate
    - Policy and Partnerships Division
  - Office of Nutrition Policy and Promotion
    - Food and Nutrition Surveillance
- Healthy Environments and Consumer Safety Branch
  - Product Safety Program, Consumer Product Safety
    - Mechanical and Electrical Division

#### Public Health Agency of Canada

- Centre for Healthy Human Development
  - Division of Childhood and Adolescence
  - Health Surveillance and Epidemiology Division
  - Healthy Communities Division
- Centre for Infectious Disease Prevention and Control
  - Community Acquired Infections Division
  - Immunization and Respiratory Infections Division
  - Surveillance and Risk Assessment Division

#### Transport Canada

- Safety and Security Group
  - Road Safety and Motor Vehicle Regulation

### Non-governmental sources

- Abbott Laboratories, Ltd.
- Bristol-Myers Squibb Company
- CHARGE Syndrome Foundation, Inc.
- Dairy Farmers of Canada
- IWK Health Centre
- Janeway Children's Hospital Foundation
- Mead Johnson Nutritionals
- Merck Frosst Canada Ltd.
- North York General Hospital
- Ontario Prader-Willi Syndrome Association
- Quebec Foundation for Research into Children's Diseases
- Striving for Excellence Fund, Mount Sinai Hospital
- The Multiple Sclerosis Scientific Research Foundation
- The Physicians' Services Incorporated Foundation

# Surveillance at Work

## Overview

The importance of surveillance to the practice of medicine cannot be overstated. Through the ongoing, systematic collection of data not only can the burden of disease be determined and interventions to prevent the occurrence of a disorder be assessed, but information collected can guide the development of health policy. Surveillance takes data to intelligence into action.

The CPSP provides an innovative means to undertake paediatric surveillance and increase awareness of childhood disorders that are high in disability, morbidity, mortality and economic cost to society despite their low frequency. Preference is given to studies that have strong public health importance or could not be undertaken any other way. All studies in the program must conform to

high standards of scientific rigour and practicality and the CPSP assures the confidentiality of all information provided to the program. The program also offers an opportunity for international collaboration with other paediatric surveillance units worldwide.

## Process

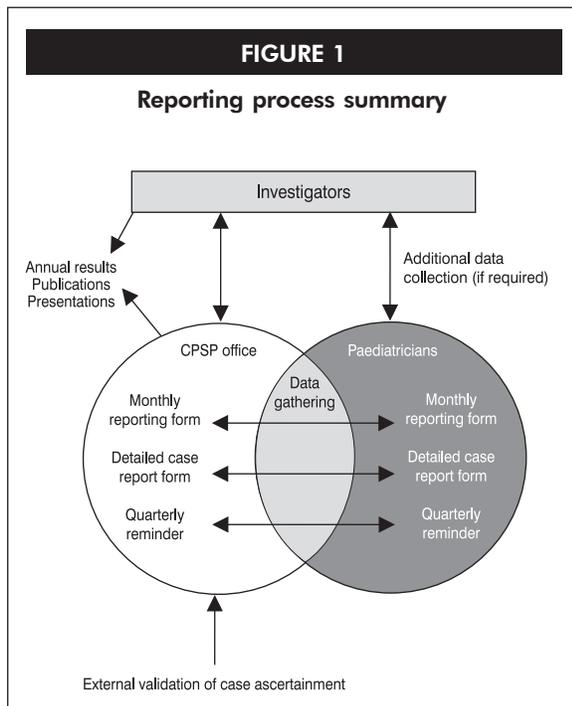
The CPSP Steering Committee oversees the program and reviews new study proposals. Upon initiation of a new study, practising Canadian paediatricians, relevant paediatric subspecialists and other health-care providers receive a summary of the protocol including the case definition and a brief description of the condition. This serves to educate and increase awareness of low-frequency conditions with high morbidity and/or mortality while providing a uniform basis for reporting. The CPSP uses a two-tiered reporting process to ascertain and investigate cases: an initial 'check-off' form and a detailed reporting form. The full process is summarized in Figure 1.

## Reporting

The 'check off' form, listing the conditions currently under surveillance, is mailed monthly to participants. Respondents are asked to indicate, against each condition, the number of new cases seen in the last month, including 'nil' reports. A 'nil' report is very important in active surveillance; the CPSP cannot simply assume that no reply means no cases.

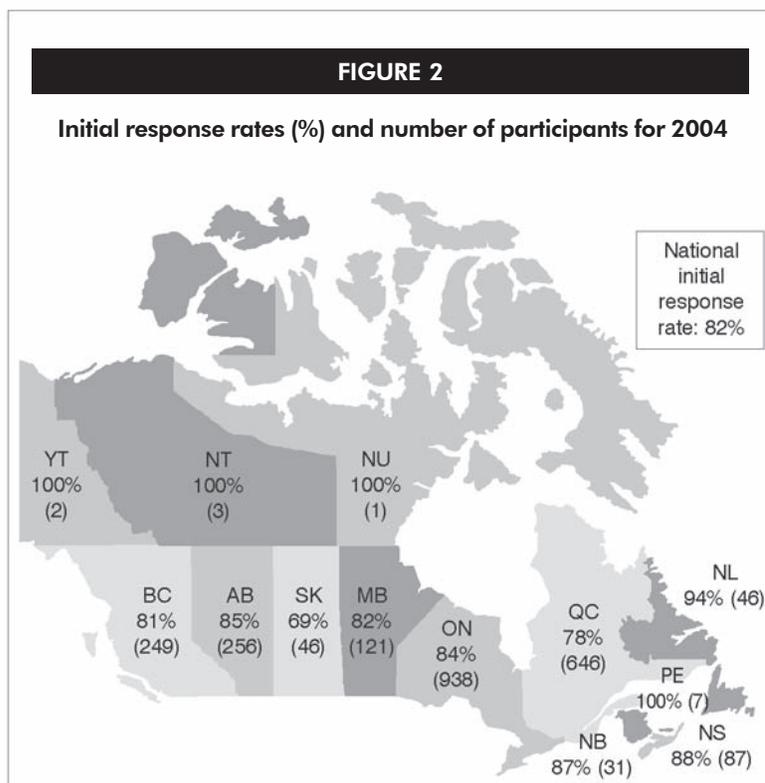
Participants report all cases meeting the case definitions, including suspect or probable cases. This sometimes leads to duplicate reports but avoids missed cases. Case ascertainment is monitored and verified by investigating duplicate reports and comparing data with relative programs or centres.

Only non-nominal patient information, such as the date of birth, sex of the child and comments on the



condition, is requested for each reported case. This anonymous information is used to identify duplicates and is entered, as a reminder, on a detailed reporting form, which is sent to the original respondent to request case-specific information. Once the detailed report is returned to the CPSP, it is forwarded to the investigator for analysis. The investigator is responsible for contacting the respondent if further information is required. The CPSP is encouraged by the 96% response rate for completion of detailed questionnaires (see Table 1 for study breakdown).

Participants who do not reply every month receive quarterly reminders. As well, information on the monthly compliance rates and the number of cases reported is mailed quarterly to all participants to keep them informed of progress.



**TABLE 1**

**2004 detailed questionnaire completion rates as of March 1, 2005**

Studies/conditions	Reported cases	Pending	% Completion rate
Acquired demyelinating syndromes of the central nervous system	66	2	97
Acute flaccid paralysis	48	0	100
Acute rheumatic fever	47	4	91
Adverse drug reactions – serious and life-threatening	67	4	94
CHARGE association/syndrome	16	0	100
Congenital rubella syndrome	8	0	100
Early-onset eating disorders	96	3	97
Lap-belt syndrome	20	2	90
Neonatal hyperbilirubinemia – severe	96	0	100
Osteogenesis imperfecta	42	4	90
Prader-Willi syndrome	38	2	95
Severe combined immunodeficiency	20	1	95
Vitamin D deficiency rickets	44	2	95
<b>Total number of cases (all studies)</b>	<b>608</b>	<b>24</b>	<b>96</b>

**Participant workload**

The program evaluation in 2003 indicated that the monthly reporting system is simple with 80% reporting that the follow-up study questionnaires were easy to complete. As only non-nominal, non-identifiable data are collected through the CPSP, 90% of those who reported a case did not hesitate to provide clinical information.

In 2004, even with a total of 608 reported cases, the majority of participants (2,088 of 2,445, 85.4%) had ‘nil’ cases to report. The importance of zero reporting must however be re-emphasized. As studies come and go, the workload shifts to different subspecialties. The number of reported cases was higher this year due to the studies on neonatal hyperbilirubinemia–severe and early-onset eating disorders and the inclusion in the program of the studies on acquired demyelinating syndromes of the central nervous system and adverse drug reactions–serious and life-threatening.

Figure 3 illustrates the number of cases reported by respondents in 2004. It shows that most participants (85.4%) had no cases to report and checked off the ‘nothing to report’ box each month, 9.7% of participants reported one case and 3.9% reported two or three cases. Only 25 participants (1%) completed four or more questionnaires. It is interesting to note that 102 of the 608 reported cases were duplicates, validating CPSP ascertainment.

The CPSP is extremely grateful that the majority of participants faithfully complete the detailed questionnaires subsequent to reporting cases. This demonstrates that they appreciate the enormous value of the scientific data collected and reinforces the insistence of the Steering Committee on short, precise and pertinent detailed questionnaires.

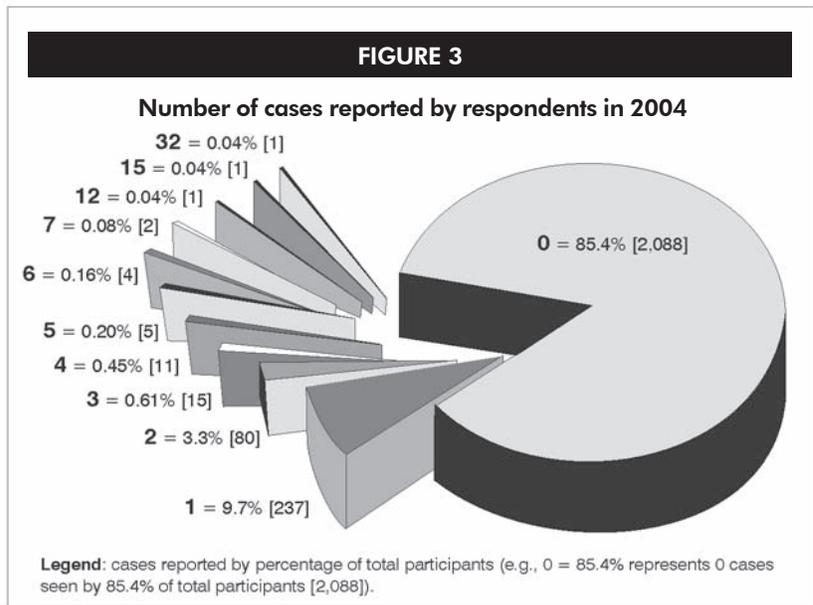
To thank paediatricians and paediatric subspecialists for their tremendous

commitment to, and support of the CPSP, 1,645 personal certificates were sent to acknowledge participation in 2004, and 340 letters of thanks went to participants who reported a case in 2004. In addition, this year’s dinner for two in the early-bird draw was awarded to Dr. Sarah Shea (NS), and the lucky winners of the year-end draws for a complimentary registration for the June 2005 CPS Annual Conference in Vancouver were Dr. Geoffrey E. Dougherty (QC), who responded for all months in 2004, and Dr. Heide Marie Schroter (AB), who completed and returned questionnaires for reported cases.

**One-time survey questions**

The CPSP is also available to survey participants as an inexpensive, one-time only tool to identify the prevalence of a problem or to answer a specific question. Once approved by the CPSP Steering Committee, the one-time survey question is sent to all participants with a monthly initial reporting form. Collected results are forwarded to the investigator for data analysis.

Results of the 2004 one-time survey questions on acquired demyelinating syndromes of the central nervous system, acute flaccid paralysis, and infant bath seats are found on page 58.



<b>TABLE 2</b>	
<b>Criteria considered for inclusion of studies</b>	
Rarity	Disorders of such low incidence or prevalence that national ascertainment of cases is needed (less than 1,000 cases a year).
Public health importance	Clearly addressing a public or paediatric health issue.
Scientific importance	Demonstrated scientific interest and importance.
Uniqueness	Proposal must demonstrate a clear need for data on a condition or disorder for which there is only limited information and for which surveillance is the most appropriate means of collecting the data.
Quality of proposal	Proposal must state clear and achievable objectives, practicability, patient confidentiality, adequate resources, clear questionnaire and method of evaluation.
Workload of paediatricians	Steering Committee must be convinced that reporting will not make excessive additional demands on the workload of paediatricians.
Priority will be given to diseases that are not currently notifiable or, if notifiable, have sufficient indication of under-notification. Investigators are expected to demonstrate that potential funding is available.	

## Investigators' corner

The CPSP provides investigators, through its timely, active surveillance system, an innovative means of identifying and obtaining data on low-frequency diseases and conditions from approximately 2,445 participants. The program is committed to a high-case ascertainment rate of over 90% and, due to follow-up reminders to non-responders, boasts a high response rate of 96% on detailed reports (Table 1). The CPSP offers an opportunity for international collaboration with other paediatric surveillance units worldwide and a chance to make a difference in the health and well-being of Canadian children and youth.

Individual researchers are encouraged to submit proposals for new studies that meet the *Criteria considered for inclusion of studies* outlined in Table 2 and follow the *Format for submission* detailed in Table 3. The Steering Committee reviews submissions at its spring and fall meetings, giving preference to studies that have either strong public health importance or could not be undertaken any other way. Studies must receive ethical approval and have funding in place before final acceptance to the program.

The CPSP is pleased to see established faculty members mentoring young researchers with their study proposals.

As previously noted the CPSP is also available to investigators as a cost-effective tool to survey participants on a one-time basis in order to identify the prevalence of a problem or to answer a specific question.

<b>TABLE 3</b>	
<b>Format for submission</b>	
<p>Proposals for new studies should include:</p> <ul style="list-style-type: none"> <li>• name of principal author</li> <li>• brief abstract of proposal</li> <li>• proposed starting date</li> <li>• proposed duration</li> <li>• question(s) to be addressed by study</li> <li>• statement of justification, including how the information could be used</li> <li>• case definition</li> <li>• expected number of cases</li> <li>• availability of ethical approval (state source of approval)</li> <li>• funding arrangements</li> <li>• identification of projected date for completion of analysis and submission for publication</li> </ul>	

## Studies timeline

<b>TABLE 4</b>			
<b>CPSP studies timeline (by end date)</b>			
<b>Study</b>	<b>Start date</b>	<b>End date</b>	<b>Total confirmed cases to December 31, 2004</b>
Group B strep	January 1996	December 1996	178
Neural tube defects	January 1997	December 1998	107
Creutzfeldt-Jakob disease	January 1997	June 1999	1
Hemorrhagic disease of the newborn	January 1997	December 2000	6
Subacute sclerosing panencephalitis	January 1997	December 2000	3
Cerebral edema in diabetic ketoacidosis	July 1999	June 2001	23
Progressive intellectual and neurological deterioration	July 1999	June 2001	59
Anaphylaxis	January 2000	June 2001	732
Hemolytic uremic syndrome	April 2000	March 2002	140
Smith-Lemli-Opitz syndrome	January 2000	December 2002	35
Hepatitis C virus infection	February 2001	January 2003	58
Neonatal liver failure/perinatal hemochromatosis	February 2001	January 2003	10
Necrotizing fasciitis	September 2001	August 2003	37
Neonatal herpes simplex virus infection	October 2000	September 2003	58
Neonatal hyperbilirubinemia – severe	July 2002	June 2004	203
Vitamin D deficiency rickets	July 2002	June 2004	69
CHARGE association/syndrome	September 2001	August 2004	90
Congenital rubella syndrome	January 1996	December 2004	9
Prader-Willi syndrome	January 2003	December 2004	31
Early-onset eating disorders	March 2003	February 2005	63
Lap-belt syndrome	September 2003	August 2005	3
Adverse drug reactions – serious and life-threatening	January 2004	December 2005	42
Osteogenesis imperfecta	January 2004	December 2005	14
Severe combined immunodeficiency	April 2004	March 2006	5
Congenital cytomegalovirus infection	March 2005	February 2007	N/A
Head injury secondary to suspected child maltreatment (abuse or neglect)	March 2005	February 2007	N/A
Acquired demyelinating syndromes of the central nervous system	April 2004	March 2007	52
Acute rheumatic fever	April 2004	March 2007	18
Medium-chain acyl-coenzyme A dehydrogenase deficiency	September 2005	August 2007	N/A
Acute flaccid paralysis	January 1996	December 2007	403
Congenital myotonic dystrophy	March 2005	February 2008	N/A

# CPSP Principal Investigators

## Surveillance studies in 2004



Dr. Brenda Banwell  
**Acquired demyelinating syndromes of the central nervous system**



Dr. Paul Varughese  
**Acute flaccid paralysis and Congenital rubella syndrome**



Dr. Christina Templeton  
**Acute rheumatic fever**



Dr. Bruce Carleton  
**Adverse drug reactions – serious and life-threatening**



Dr. Kim Blake  
**CHARGE association/syndrome**



Dr. Leora Pinhas  
**Early-onset eating disorders**



Dr. Claude Cyr  
**Lap-belt syndrome**



Dr. Michael Sgro  
**Neonatal hyperbilirubinemia – severe**



Dr. Leanne Ward  
**Osteogenesis imperfecta and Vitamin D deficiency rickets**



Dr. Glenn Berall  
**Prader-Willi syndrome**

## New studies in 2005



Marene Gatali  
**Severe combined immunodeficiency**



Dr. Wendy Vaudry  
**Congenital cytomegalovirus infection**



Dr. Craig Campbell  
**Congenital myotonic dystrophy**



Morag Mackay  
**Head injury secondary to suspected child maltreatment (abuse or neglect)**



Dr. Chitra Prasad  
**Medium-chain acyl-coenzyme A dehydrogenase deficiency**

# Surveillance Studies in 2004

## Acquired demyelinating syndromes of the central nervous system

(April 2004 to March 2007)

### Highlights

- Demyelination is not as rare as previously thought as 52 cases were confirmed in the first nine months of the study.
- Four confirmed cases have a current diagnosis of multiple sclerosis.
- The majority (80.7%) of confirmed cases required treatment and 96% had brain MRI performed.
- Reporting physicians discussed the possibility of recurrent demyelination with patients and families in 86% of first-time cases.

### Background

Acquired demyelinating syndromes (ADS) of the CNS in childhood are serious events and may not be as rare as previously thought. The varied clinical phenotypes of initial acute CNS demyelination, termed clinically isolated syndromes (CIS), include optic neuritis, transverse myelitis, hemisensory or hemi-motor syndromes, cerebellar or brainstem dysfunction, alone (monosymptomatic CIS), in combination (polysymptomatic CIS), or associated with encephalopathy (acute disseminated encephalomyelitis, ADEM). Advancing our understanding of demyelination in children is of the utmost importance given that these children may suffer significant acute and long-term morbidity, and are at risk for recurrent demyelination characterizing the chronic autoimmune disease multiple sclerosis (MS).

This study will gather case-specific data to document the clinical features, epidemiological characteristics,

familial autoimmune profile, and the current medical care practices provided to children with ADS. This initiative will provide a measure of the impact of CNS demyelination on Canadian children and aims to enhance care of affected children by increasing awareness among Canadian paediatricians of CNS demyelination, and of MS in particular, facilitating prompt and specialized care for children with this disease.

### Objectives

- 1) To increase awareness and understanding of paediatric CIS and MS among Canadian paediatricians.
- 2) To define the incidence of the various forms of paediatric CIS in Canadian children.
- 3) To evaluate the epidemiological features and familial autoimmune profile of children with CIS.
- 4) To describe current treatments offered to children with CIS across Canada, with attention to differences in treatment protocols across regions and between community and tertiary care facilities.
- 5) To evaluate paediatric and paediatric neurologist practices in discussing with families the possibility of MS following CIS in childhood.

### Case definition

Children less than 18 years of age with one of the following syndromes are reported:

- Acute loss of vision (**optic neuritis**): decreased visual acuity of one or both eyes, typically maximal over a period of days, often associated with pain. CT/MRI may show swelling and abnormal signal of optic nerves.
- Spinal cord dysfunction (**transverse myelitis**): weakness and/or numbness of both legs +/- arms, often associated with bladder retention with maximal deficits four to 21 days after symptom onset. MRI may demonstrate swelling and/or abnormal signal in the spinal cord.

- Acute neurological deficits: **acute neurological dysfunction** (i.e., weakness, numbness/tingling, loss of balance, impaired eye movements, double vision, poor coordination) maximal within four to 21 days after onset associated with MRI evidence of at least one area of abnormal white matter signal of the brain or spinal cord. Level of consciousness should be normal, and fever or neck stiffness absent.
- Acute disseminated encephalomyelitis (**ADEM**): acute neurological deficits (weakness, numbness, loss of balance) associated with at least two of the following: (1) viral prodromal illness within the last 28 days; (2) fever; (3) stiff neck; (4) headache; (5) altered level of consciousness or behaviour; or (6) seizures. MRI shows multiple areas of abnormal signal in the white matter.

**Exclusion criteria**

- Demyelination of the peripheral nervous system (i.e., Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy)
- Leukodystrophies (i.e., metachromatic leukodystrophy, adrenoleukodystrophy, etc.) or mitochondrial disease
- Active CNS infection (i.e., bacterial meningitis, herpes simplex encephalitis, Lyme disease, HIV, HTLV-1, West Nile virus)
- Radiation/chemotherapy associated white matter damage.

**Results**

**Demographic and incidence data**

There were 65 cases of CNS demyelination reported between April 1 and December 31, 2004. Of these reports, 52 cases met inclusion criteria, four cases are

TABLE 5				
Acquired demyelinating syndromes of the central nervous system cases April 1 to December 31, 2004				
Reported	Duplicates	Excluded	Under review	Confirmed
65	8	1	4	52

pending review, eight were duplicate reports, and one case was discarded (Table 5).

The majority of confirmed ADS cases were from Ontario (37/52, 71%). Six other provinces each had less than five cases (BC, MB, NB, NL, NS and QC).

The mean age of confirmed ADS cases is 10.6 years (range 0.6–17.4 years) and the female to male ratio is 1.5:1 (31 females, 21 males).

**Epidemiological and familial autoimmune data**

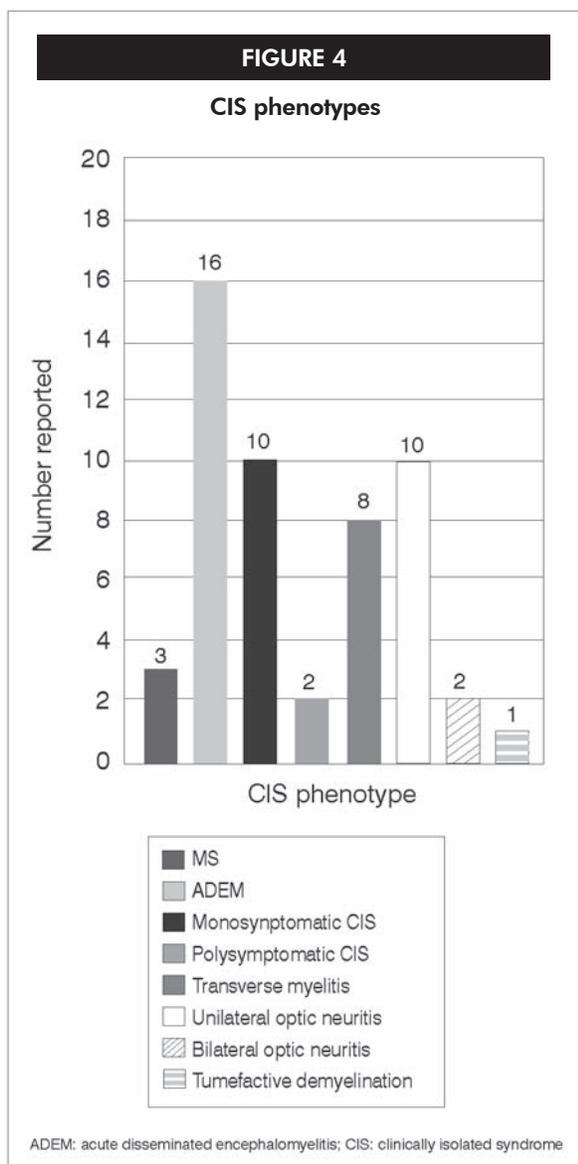
Most of the children reported were born in Canada (90%, 47/52), with one child in the United States and four children born outside North America. Although the majority of patients reported ethnicity/ancestry as ‘White/European’ (67%), Asian and mixed-Asian race children were identified (17%). Other ethnic groups identified include Black, Hispanic, Native Canadian and other mixed ethnicities. There were three cases in which ancestry/ethnicity was not reported.

Fifteen percent (15%, 8/52) of confirmed cases reported a family history of MS, with two unconfirmed reports of family medical history. In nine cases, family history of other autoimmune conditions was reported, such as thyroiditis, juvenile diabetes mellitus, and systemic lupus.

**Clinical features and paediatric practices**

Figure 4 illustrates the various clinical phenotypes seen with the reported cases of acute demyelination. The majority of ADS cases (31%) were ADEM, followed by cases of monosymptomatic CIS (19%), unilateral optic neuritis (19%), and transverse myelitis (15%).

Treatment for the demyelinating event was required in all but ten cases. This was reported by indicating whether intravenous or oral steroids were given, or if intravenous immunoglobulin therapy was prescribed. Combinations of the aforementioned medications were necessary in half of the patients requiring treatment (21/42).



Fifty (96%) confirmed cases had brain MRIs completed, with 41 of those 50 showing abnormal white matter changes. Seven cases reported an infection preceding the demyelinating event and within one month of the demyelinating event, and two of those seven cases received a vaccination within the same period, prior to the event. Eighty-three percent (83%, 43/52) of the confirmed cases were first-time acute demyelinating syndromes and in 86% of these first-time cases, recurrent demyelination was discussed with the patients and families.

## Conclusion

There was an average of approximately six cases reported per month in the first nine months of this study. Based on annual estimates from members of the Paediatric Demyelinating Disease Network (PDDN), it is estimated that 107 children present with acute demyelination each year in paediatric centres across Canada. With the majority of reports coming from Ontario, and with lower than expected numbers of cases reported to the CPSP thus far, there may be under-reporting or unidentified cases of demyelination across the country.

The ages of the children reported (ranging from 0.6 to 17.4 years) emphasize the importance of identifying and understanding these events as these children may experience significant short and long-term deficits, which can impact their overall development.

The majority of these patients required treatment for their demyelinating event and almost all confirmed cases underwent brain MRI. The detailed reporting forms do not include a question about MRI of the spinal cord. MRI of the brain may be normal while inflammation will be seen in imaging of the spinal cord for patients with transverse myelitis.

For these reported cases, there exists a true risk of recurrent demyelination and the possible diagnosis of MS, underscoring the importance of prompt diagnosis and initiation of appropriate treatment. From the CPSP reporting, this risk is being discussed with the patients and families showing that reporting physicians are aware of this possibility for children presenting with ADS. A further effort to raise awareness of these syndromes is needed.

## Principal investigator

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\* Representing the Paediatric Demyelinating Disease Network (22 paediatric care facilities across Canada)

# Acute flaccid paralysis

(January 1996 to December 2007)

## Highlights

- No wild polio virus infection has been detected in Canada since 1988.
- The number of AFP cases reported for 2003 and 2004 was lower than previous years.
- Guillain-Barré syndrome accounts for at least 71% of confirmed AFP cases.
- Stool investigations for poliovirus are essential.
- No *Campylobacter* organisms were detected in stool specimens examined.

## Background

The elimination of indigenous wild poliovirus transmission in Canada, and the rest of the American region, was certified in September 1994. However, until global polio eradication is attained there remains an ongoing risk of wild poliovirus importation from polio-endemic regions. Consequently, active surveillance of acute flaccid paralysis (AFP) in children less than 15 years of age is used to monitor potential cases of paralytic poliomyelitis. Based on an estimated background annual incidence of one AFP case per 100,000 in a population less than 15 years of age in the absence of wild poliovirus transmission, the estimated minimum number of AFP cases in Canada is 57 cases per year. AFP surveillance in Canada was initiated in 1991 through the IMPACT (Immunization Monitoring Program, ACTive) network of paediatric tertiary care centres, and, since 1996, has been implemented through the CPSP. This report presents the results of AFP surveillance in 2004 and compares them to those from previous years.

## Objective

The objective of AFP surveillance is to identify AFP cases (including Guillain-Barré syndrome [GBS]) in children less than 15 years of age to rule out paralytic poliomyelitis and thereby monitor the polio-free status of Canada.

TABLE 6

### World Health Organization quality assurance criteria for acute flaccid paralysis surveillance

- 1) one case of AFP per 100,000 children under 15 years of age
- 2) adequate poliovirus stool cultures in at least 80% of AFP cases

## Case definition

Acute onset of focal weakness or paralysis characterized as flaccid (reduced tone) without other obvious cause (e.g., trauma) in children less than 15 years of age. Transient weakness (e.g., post-ictal weakness) should not be reported.

## Results and discussion

In 2004, the CPSP received 48 initial AFP reports that included 35 (73%) confirmed cases, 11 duplicates, and two exclusions (Table 7). Thirty-five confirmed cases represent a rate of 0.57 per 100,000, which is below the minimum estimated background rate of one case per 100,000 children less than 15 years of age, or 57 cases. With the anticipated ‘late reports’ for the current year, the final number is likely to be slightly higher but will be well below the World Health Organization (WHO) targeted rate.

There was an equal split in the sex of the cases (18 males and 17 females). The cases ranged in age from nine months to 14 years, (median 6.3 years) with a mean four years in 2004. Table 8 shows the age distribution of AFP cases reported in 2004 compared with cases reported from 1996 to 2003. Overall, the age distribution is similar throughout the reporting period.

TABLE 7

### Acute flaccid paralysis cases in 2004

Reported	Duplicates	Excluded	Under review	Confirmed
48	11	2	0	35

TABLE 8									
Age distribution of AFP cases reported to the CPSP									
Age group (years)	Number of cases								
	1996	1997	1998	1999	2000	2001	2002	2003*	2004
0 – 1	2	—	2	3	2	8	10	5	5
2 – 5	11	13	15	18	24	18	16	17	14
6 – 10	9	12	18	23	22	14	11	7	9
11 – <15	8	10	8	17	13	14	6	15	7
<b>Total</b>	<b>30</b>	<b>35</b>	<b>43</b>	<b>61</b>	<b>61</b>	<b>54</b>	<b>43</b>	<b>44</b>	<b>35</b>

\* Includes two delayed reports not included in the CPSP 2003 Results.

Although most Canadian children today are vaccinated against polio, only ten of the 35 cases (28.6%) had documentation of routine childhood immunization, and all had received age-appropriate polio immunization. Four cases (11.4%) indicated that they had up-to-date immunization for polio, although no polio vaccine-specific information was available on the detailed case report forms.

**Virological investigation for polio or other enteroviruses**

A total of 21 (60%) cases had stool examination; virology was not done or the status was unknown for 14 (40%) cases. However, only 15 cases (43%) had adequate stool investigation for the isolation of poliovirus or non-polio enteroviruses (i.e., stool specimen collected within two weeks of the onset of paralysis). For six cases, although stool specimens were collected, it was after two weeks of onset of paralysis. There was no positive identification for polioviruses or other enteroviruses. It is encouraging to note that the proportion of cases who had polio-specific stool investigation has increased from 26% in 1998 to 48% in 2003, with a slight decrease (43%) in 2004 (Figure 5). These rates of adequate stool investigation remain significantly lower than the WHO target of 80%. Eleven throat swabs and 18 cerebrospinal fluid (CSF) specimens were collected for viral isolation. Results for ten throat swabs and 14 CSF specimens were available; none were positive for poliovirus. Eighteen (18) of the

35 (51%) stool specimens were also tested for *Campylobacter* organisms, but all were negative.

**Neurological investigations**

Neurological investigation consisted of at least one or more of the following: CSF analysis (protein,

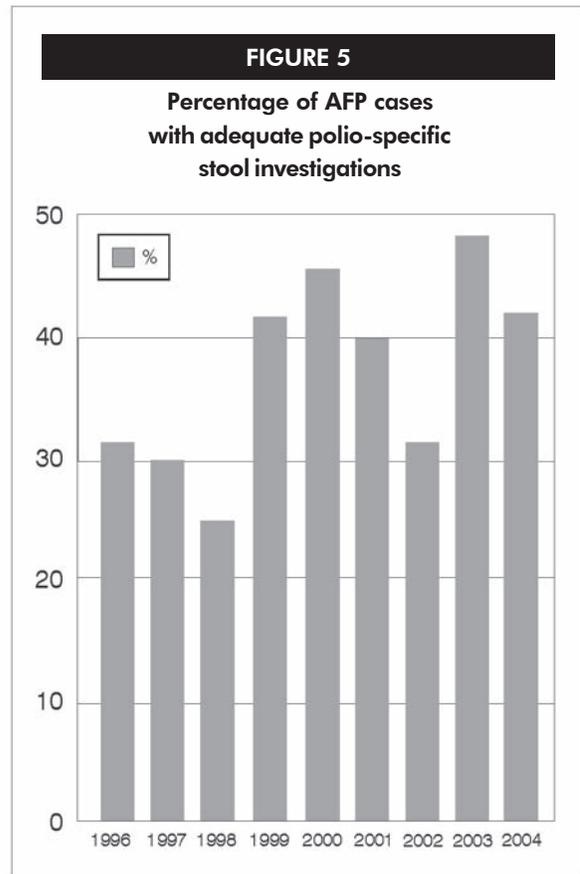


TABLE 9

## Neurological diagnosis of AFP cases reported to the CPSP

Final diagnosis	Number of cases								
	1996	1997	1998	1999	2000	2001	2002	2003*	2004
Polio	0	0	0	0	0	0	0	0	0
Guillain-Barré syndrome	21	29	34	50	49	42	33	33	25
Transverse myelitis	6	2	6	7	4	8	7	4	7
Encephalitis/encephalomyelitis/encephalopathy	1	1	1	—	—	—	—	3	—
Myelopathy	—	1	—	—	—	—	—	—	—
Radiculopathy/radiculoneuritis	1	1	—	—	—	1	1	—	—
Plexitis/lumbosacral plexitis	—	—	—	2	—	—	—	1	—
Brachial neuritis	—	—	—	1	—	—	—	—	—
Rhombomyelitis	—	—	—	1	—	—	—	—	—
Other	—	—	—	—	8	3	2	3	3
Not specified/undetermined diagnosis or etiology	1	1	3	—	—	—	—	—	—
<b>Total</b>	<b>30</b>	<b>35</b>	<b>44</b>	<b>61</b>	<b>61</b>	<b>54</b>	<b>43</b>	<b>44</b>	<b>35</b>

\* Includes four delayed reports not included in the CPSP 2003 Results.

glucose, white blood cells, neutrophils, lymphocytes, and red blood cells), nerve conduction studies, electromyography, MRI or CT scan. Abnormal findings compatible with the neurological diagnosis were reported for one or more of the tests done. Twenty-one of the 26 (81%) CSF specimens indicated some abnormal findings. MRI or CT scanning was done for 23 cases (66%); for MRI, 14/23 (61%) showed some abnormality. Electromyography and/or nerve conduction studies were done for 25 (71%) cases; 23 (92%) of these cases had abnormal findings.

Guillain-Barré syndrome was the final neurological diagnosis in 25 (71%) cases. These included axonal GBS, GBS/muscular dystrophy, motor variant GBS and acute motor axonal myopathy-variant of GBS. Transverse myelitis was found in five (14%) and transverse myelitis and acute disseminated encephalomyelitis (ADEM) was found in two cases (Table 9). The remaining three diagnoses included neuroborreliosis, leukodystrophy and ADEM secondary to 'cat scratch fever'.

Hospitalization was required in 33 of the 35 (94%) cases for periods ranging from one to 37 days (mean of seven days). Of the 35 cases, three (9%) recovered fully, five (14%) had recovered partially with residual weakness, and for six (17%) recovery status was unknown at 60 days after the onset of paralysis. None of the clinical specimens tested, i.e., stool, nasopharyngeal or cerebrospinal fluids, were positive for poliovirus infection.

## Conclusions

The 35 AFP cases identified to date for 2004 are below the expected rate in Canada, according to the World Health Organization criteria. For the corresponding period for 2003, a total of 44 cases reported were confirmed.

It is interesting to note that the AFP reporting rate improved since the introduction of paediatrician-based reporting through the CPSP from 0.5 per 100,000 children less than 15 years in 1996 (30 cases), to 1.04 per 100,000 in 2000 (61 cases);

however, for unknown reasons the rate has decreased since then. Undoubtedly, the expansion of AFP surveillance to the CPSP has improved the completeness of surveillance by ensuring that AFP cases seen at non-tertiary hospitals are reported in addition to those cases admitted to paediatric tertiary care hospitals and reported through IMPACT.

The decline in the number of AFP cases documented by the CPSP over the past four years might be due to under-reporting of cases or a reflection of current epidemiological trend; both need to be further investigated.

A major area in which the AFP surveillance could be improved is the performance of polio-specific investigations and timely reporting of results. While neurological investigations provide supporting evidence for the final diagnosis in the majority of reported AFP cases, polio-specific laboratory investigations remain vital for the evaluation of all cases, including those in which poliomyelitis is not being considered as a possible diagnosis. Negative results of appropriate polio-specific investigations are as important as a positive result in AFP case evaluations. The single most important laboratory investigation, recommended by the national Working Group on Polio Eradication, to confirm or to rule out a diagnosis of paralytic poliomyelitis, is a stool specimen collected within two weeks of onset of paralysis for isolation of wild or vaccine strain poliovirus; specimens may be collected up to six weeks after the onset of paralysis, although after two weeks the sensitivity of virus isolation decreases. The examination of paired serum samples for evidence of a four-fold or greater rise in poliovirus antibody titre in paired sera and/or the presence of poliovirus-specific IgM antibody in a single serological specimen further enhance the evaluation of cases.

### Principal investigator

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### Acknowledgement

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# Acute rheumatic fever

(April 2004 to March 2007)

## Highlights

- Acute rheumatic fever is extremely rare in paediatrics.
- Affected children have significant morbidity: eight children with carditis and five with Sydenham's chorea.
- Multiple medication needs are documented.

## Background

Acute rheumatic fever is a post-infectious collagen vascular disease affecting the heart, joints and central nervous system. It follows untreated Group A streptococcal (GAS) pharyngitis after a latent period of approximately three weeks. It does not occur after other GAS infection, such as skin infection (impetigo). Worldwide, it remains the most common cause of acquired heart disease in children, but the incidence is widely variable from region to region, with the vast majority of cases now occurring in developing countries.

The incidence of acute rheumatic fever in developed countries has decreased dramatically since its last peak in the 1970s, but it has not disappeared, and remains an important public health issue. The reason for its decrease is not fully understood. The decline in incidence in the early 20<sup>th</sup> century had already begun prior to the introduction of effective antimicrobial agents, but common use of penicillin to treat symptomatic sore throat may have contributed to the decline somewhat (Massell et al, 1998). Socio-economic factors, such as overcrowding and low income, are known to be significant risk factors (WHO, 1998). The majority of cases of rheumatic fever follow cases of pharyngitis due to specific M serotypes of GAS, most commonly 1, 3, 5, 6, 18, 19 and 24 and spontaneous fluctuation of the prevalence of these serotypes is known to occur (Schwartz et al, 1990, Colman et al, 1993).

Rheumatic fever is not a reportable condition in Canada, and in the current era of evidence-based, judicious use of antibiotics, ongoing surveillance of this now rare but serious condition is crucial. Rheumatic heart disease is a lifelong complication of the condition, which can lead to ongoing medical and surgical needs and can interfere with employment, causing significant socio-economic impact. However, the risk of developing rheumatic fever must be balanced against the risk of encouraging microbial antibiotic resistance, which is a growing problem in all developed nations and carries its own impact.

There is no current Canadian literature to suggest incidence. This is a sufficiently rare condition that only a national reporting system could gather statistically significant numbers.

## Objectives

- 1) To determine the incidence of rheumatic fever among Canadian children.
- 2) To determine the relationship between modern rheumatic fever and demographic features, such as overcrowding and low household income.
- 3) To describe current Canadian treatment practices.
- 4) To determine the morbidity and mortality of first episode rheumatic fever in Canada.

## Case definition

Report any child up to and including 18 years of age that meets the most recent modification of the Jones criteria for diagnosis of an initial attack of rheumatic fever (Table 10).

The definition of carditis requires clinical evidence of cardiac involvement in the form of a pathological murmur, pericarditis, or congestive heart failure. Current literature is divided as to whether silent echocardiographic findings should be included (Ozkutlu, 2001); the questionnaire includes this information, but the case definition remains faithful to current international consensus requiring clinical manifestations.

TABLE 10	
Guidelines for the diagnosis of an initial attack of rheumatic fever, Jones criteria	
Major manifestations	Minor manifestations
Carditis Polyarthritits Chorea Erythema marginatum Subcutaneous nodules	Clinical Arthralgia Fever Laboratory findings Increased acute phase reactants: - Increased erythrocyte sedimentation rate - Increased C-reactive protein Prolonged P-R interval
<p>All cases, except Sydenham’s chorea, will require documentation of antecedent group A streptococcal infection, either by positive throat culture, rapid antigen test, or an elevated or rising antibody titre. Antistreptolysin O titre measurement is the preferred test to distinguish recent streptococcal infection from chronic pharyngeal carriage.</p> <p>If there is evidence of recent streptococcal infection, the presence of two major manifestations or one major and two minor manifestations will be considered diagnostic.</p>	

## Results

### Demographic data

Of the 18 cases confirmed to date, six were in Ontario, five in Quebec and less than five cases in five other provinces (BC, MB, NL, NS and SK). The average age at diagnosis was 10.6 years. There were 12 girls and six boys. Of those cases in whom numbers of individuals in the household were reported, the average total occupancy of the

TABLE 11				
Acute rheumatic fever cases April 1 to December 31, 2004				
Reported	Duplicates	Excluded	Under review	Confirmed
45	11	6	10	18

household was 5.2, with the average number under the age of 18 being 2.8. However, reporting paediatricians were able to supply this information in just over half of the cases. All children except two were born in Canada, and one visited a developing country just prior to diagnosis.

### Systems affected

Eight patients had carditis meeting clinical criteria, with four of them requiring medical therapy for congestive heart failure at the time of reporting. Therapy consisted of digoxin, ACE inhibitors, beta blockers and diuretics. None required surgical therapy. Twelve patients had polyarthritits meeting clinical criteria; it was migratory in ten of those cases. All were receiving anti-inflammatory medication at the time of reporting. Medications being used included naproxen, prednisone, aspirin, and ibuprofen. Five patients had Sydenham’s chorea; three reports included documentation of medical therapy. Agents used were risperidone, valproic acid, and clonazepam. Two patients had erythema marginatum, and two patients had subcutaneous nodules.

### Long-term prophylaxis

In two cases, follow-up data on antibiotic prophylaxis delivery was unavailable. In the remaining 16 cases, all are receiving prophylaxis. Two are receiving monthly IM injections of benzathine penicillin. Two are receiving erythromycin because of penicillin allergy. The remaining 12 patients are all receiving oral penicillin twice daily.

### Conclusion

The first year of this study has shown, as expected, that acute rheumatic fever in children 18 years and younger is an extremely rare condition, with only 18 confirmed cases documented nationally. Within this small group, there is significant morbidity and a requirement for multiple medications. There is a continuing need for vigilance so that ARF is prevented whenever possible.

It is hoped that ultimately this study will provide valuable data on the incidence of rheumatic fever that can be taken into consideration in guidelines for treatment of pharyngitis, keeping the relevant risks balanced.

### Principal investigator

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Proton Rahman, MD, Memorial University of Newfoundland

## Adverse drug reactions – serious and life-threatening

(January 2004 to December 2005)

### Highlights

- The majority of suspected ADRs were previously recognized reactions.
- The drugs most frequently reported in suspected ADRs were carbamazepine, valproic acid, amoxicillin, and cefprozil.
- Because the majority of drugs are not tested in the paediatric population, post-marketing surveillance of ADRs is essential to identify reactions not recognized prior to drug licensure.

### Background

Adverse drug reactions (ADRs) have been estimated to rank as one of the top ten leading causes of death and illness in the developed world. Children may be at greater risk of ADRs than adults. Alarming, between 13.7% and 16.6% of paediatric hospitalizations are a result of ADRs, and 27.9% of these reactions are severe. There is a remarkable lack of understanding of causation, and therefore limited ability to avoid or prevent these occurrences.

Health Canada, through the Canadian Adverse Reaction Monitoring Program, received 1,209 reports of suspected ADRs in children between January 1, 1998 and May 30, 2002. However, this voluntary reporting system reflects only a small proportion of significant ADRs. Health-related accreditation bodies estimate that 95% of all ADRs in Canada are not reported. Systematic examination of medical outcomes is clearly

impossible if only 5% of the actual reactions are reported.

More than 75% of prescribed pharmaceuticals on the market in North America have never been tested in paediatric populations and are used without adequate guidelines for safety or efficacy. Clinical practice focused on adjusting dosage to account for smaller body mass, with the assumption that clinical effects would be equivalent to those observed in adults. It is for these reasons that children worldwide are described as “therapeutic orphans” and are placed at an increased risk of therapeutic failure, while ADRs continue to cause unnecessary disability and death.

It is now understood that a host of biological, developmental and behavioural factors impact the safety and effectiveness of pharmaceuticals when used in paediatric patients. As a result, newborns, infants and children who require medication for acute, chronic and life-threatening diseases are at risk of a range of ADRs from lack of efficacy and minor ADRs through to severe morbidity and death.

**Objectives**

- 1) Increase reporting by paediatricians (CPSP) of serious and life-threatening adverse drug reactions that occur in children aged 18 years or less, not currently captured by existing spontaneous reporting systems.
- 2) Determine the usefulness of the data collected by CPSP for meaningful analysis and interpretation.
- 3) Identify public health concerns regarding adverse drug reactions in the paediatric population.

**Case definition**

Serious and life-threatening adverse drug reactions\* in an infant or child 18 years or less, associated with the use of prescription, non-prescription, biological (immunoglobulin) products, complementary medicine (including herbals), and radio-pharmaceutical products. Report even if you

are not certain if the product caused the adverse reaction or you do not have all the reporting details.

**Exclusions:** Do not report reactions due to medical devices, blood products (platelets, red cells, single donor plasma), vaccines, poisonings or self-administered overdoses.

\* *Noxious and unintended severe response to a drug which occurs at any dose and results in emergency observation, hospitalization, persistent or significant disability, or death.*

**Results**

During 2004, 64 reports of suspected ADRs were submitted to the CPSP. For these, 53 detailed reports were received. Eleven of the detailed reports were excluded due to lack of information or failure to meet the inclusion criteria. In total we examined 42 reports of paediatric suspected adverse drug reactions in our analysis (Table 12).

Fourteen reports concerned females, 25 concerned males, and in three cases the gender was not mentioned. The majority of reported cases involved patients between six and 18 years of age. The patient’s age was not reported in one case included in the analysis, but it was judged that the drug had been administered to a child. The majority of patients (78%) were Caucasian, one child was Bangladeshi, one Kurdish and one a native Canadian. In six reports no race was reported.

**Drugs responsible for suspected adverse drug reactions**

In 36 cases, just one active ingredient was suspected of causing the reaction; in six cases two suspected

TABLE 12				
Adverse drug reactions – serious and life-threatening cases in 2004				
Reported	Duplicates	Excluded	Under review	Confirmed
64	0	11	11	42

TABLE 13	
Suspected active ingredients (n=35) in ADR reports (n=48)	
Active ingredient	Reports
Acetylsalicylic acid	1
Amoxicillin	1
Ampicillin	4
Aprotinin	1
Azithromycin	1
Carbamazepine	1
Cefprozil	4
Clarithromycin	3
DDAVP	1
Dexamethasone	1
Dextromethorphan	1
EES*	1
Ethinyl estradiol	1
Etoposide	1
Haloperidol	1
Ibuprofen	1
Infliximab	2
Isotretinoin	2
Lamotrigine	1
Levonorgestrel	1
Methylene blue	1
Methylphenidate	1
Naproxen	1
Paraldehyde	1
Peg L-asparaginase	1
Pentobarbital	1
Phenobarbital	1
Pimozide	1
Propylthiouracil	1
Quetiapine	1
Risperidone	1
Teniposide	1
Topiramate	1
Trimethoprim	1
Valproic acid	4

\* Erythromycin ethylsuccinate

generic drugs were involved. Involvement of 35 unique active ingredients was reported. The suspected drugs most frequently reported were: carbamazepine, valproic acid, amoxicillin, and cefprozil (Table 13). Examples of reported reactions suspected to be associated with valproic acid included necrotizing pancreatitis, thrombocytopenia and ataxia, whereas carbamazepine reactions were Steven-Johnson syndrome, angioedema, vascular rash, hepatosplenomegaly/hepatitis and blood disorders (neutropenia, thrombocytopenia, eosinophilia).

TABLE 14	
Patient outcomes resulting from suspected ADR	
Outcome	Times reported*
Life-threatening reaction	10
Hospitalization	20
Hospitalization prolonged due to ADR	12
Disability	1
Required intervention to prevent damage/ permanent impairment	15
Died	0
Unknown	8
<b>Total</b>	<b>66</b>

\* Possibility of overlap

### Patient outcomes resulting from reported suspected ADRs

Eighty-one percent (81%) (n=34) of the reports of suspected adverse drug reactions provided information about patient outcome (Table 14). Of note is that more than one outcome was reported for most cases. There were no deaths associated with any of the reported cases.

At the time of reporting, the recovery status of patients was: 20 recovered, five not recovered and 17 unknown or not reported. In 26 cases it was reported that the reaction abated after the drug was stopped or dose reduced. There were six reported cases of drug re-challenge; in four cases the drug reaction reappeared and in two cases it did not. There were no reports of other family members having a similar reaction to the drug suspected of causing the ADR.

### Discussion

The majority of suspected ADRs were previously recognized reactions that had been published in the medical literature and associated with the specific drug or drug class. The two most frequently reported drug classes involved were anticonvulsant and antibiotic. No death was reported but ten life-threatening events were reported and one child remains disabled. Thorough analysis of the data will

be undertaken over the next year to establish the usefulness of the data collected by the CPSP for meaningful analysis and interpretation, including the level to which the CPSP identified serious life-threatening ADRs not captured by the existing spontaneous reporting system.

### Conclusion

In many cases, information collected was incomplete. To adequately assess causality, it is critical that clinicians be vigilant at answering all questions: drug name, dose, strength, dosage form, route of administration, therapy dates, date of suspected ADR, concomitant drugs and re-challenge information. Without full collection of these data, causal relationships between drug and reaction cannot be demonstrated.

In general, the need for increased reporting and the lack of complete information about the reactions experienced make drawing definitive conclusions about causality or patient safety impossible. Because the majority of drugs are not tested in the paediatric population, post-marketing surveillance of adverse drug reactions is essential in helping to identify possible adverse reactions not recognized prior to drug licensure.

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## CHARGE association/ syndrome

(September 2001 to August 2004) Final Report

### Highlights

- The CHARGE study identified 100 individuals, the largest epidemiological cohort in the literature.
- Refinement of the diagnostic clinical criteria based on study results is proposed.
- Behavioural issues, osteopenia/osteoporosis and pubertal delay are common in adolescents and adults with CHARGE.

### Background

CHARGE association/syndrome (CHARGE A/S) is a constellation of a number of congenital anomalies that was first given the acronym CHARGE (Coloboma, Heart Defect, Choanal Atresia, Retarded Growth and Development, Genital Hypoplasia, Ear Anomalies/Deafness) in 1981.

Over the past 15 years, the specificity of this pattern of malformations has reached the level that many clinicians now consider it to be a discrete recognizable syndrome (Graham JM, *Am J Med Genet* 2001; 99:120-3). The clinical criteria originally proposed needed further refinement. The revised consensus clinical diagnostic criteria by Blake et al, 1998, incorporated both major and minor features for CHARGE A/S and have been documented to enhance clinical diagnosis and facilitate research efforts. These clinical criteria consist of four major characteristics: coloboma, choanal atresia, characteristic ear anomalies, cranial nerve dysfunction (facial palsy, vestibular dysfunction, and swallowing difficulties) and seven minor features: heart defect, orofacial cleft, genital hypoplasia, growth deficiency, developmental delay, tracheoesophageal fistula and a distinctive facial appearance. The diagnosis is firmly established when all four major or three major and three minor clinical

criteria are present. Some of the clinical features are difficult to detect in infants, and as the major characteristics are rare in other conditions, the CHARGE A/S diagnosis needs to be considered in any individual who has one or two major clinical criteria and several minor characteristics. To define CHARGE A/S in these individuals, a cranial CT or MRI scan may show hypoplasia of the semicircular canals and/or cochlea and/or choanal atresia or stenosis. High resolution chromosome studies, fluorescence *in situ* hybridization (FISH) for 22q11 deletion and the subtelomeric deletion FISH testing help to rule out any chromosomal abnormalities accounting for the multiple congenital anomalies. An increase in paternal age of CHARGE A/S children has been recognized as a risk factor and needs to be confirmed. Recently, mutations in a new member of the chromodomain gene family (CHD7) on chromosome 8 were identified in CHARGE individuals, confirming a genetic etiology (Vissers LE et al, *Natl Genet* 2004; 36:955-7).

The purpose of this study was to determine the incidence and prevalence of CHARGE A/S in Canada, as the true incidence is unknown. As CHARGE A/S presents with a wide spectrum of clinical severity, mildly affected patients may also be diagnosed and can be followed prospectively. The review article entitled, "CHARGE association: An update and review for the primary paediatrician" (Blake et al, *Clin Pediatr* 1998; 37:159-74) summarizes current understanding of the management of this complex and chronic multiple congenital anomaly, giving physicians a guide to the management of CHARGE A/S.

**Objectives**

- 1) To determine the incidence and prevalence of CHARGE A/S in Canada by ascertaining all identified cases of CHARGE A/S (old and new).
- 2) To obtain demographic and medical information on patients with CHARGE A/S and assemble a database to answer research questions.
- 3) To follow, developmentally and behaviourally, an identified group of CHARGE A/S infants who

have been diagnosed at an early age and have obtained early intervention services. Will early recognition and treatment of these infants improve their clinical and behavioural well-being?

- 4) To answer future research questions.

**Case definitions**

Infant/child/adult with four major clinical criteria or three major and three minor clinical criteria.

- Major inclusion clinical criteria: coloboma, choanal atresia, characteristic ear abnormalities, cranial nerve dysfunction.
- Minor inclusion clinical criteria: genital hypoplasia, developmental delay, cardiovascular malformations, growth deficiencies, orofacial cleft, tracheoesophageal (TE) fistula, characteristic face.

**Exclusion criteria**

Velocardiofacial syndrome and DiGeorge Sequence should be excluded using FISH test (fluorescent *in situ* hybridization) to exclude 22q11 deletion.

**Results**

**Incidence**

In three years of surveillance, 100 individuals with confirmed CHARGE A/S, 55 males and 45 females, were reported. Table 15 not only provides data on case reports, but also demonstrates the high rate of duplicates. The provincial distribution of confirmed cases reported during the study period is summarized in Table 16 and continues to demonstrate a provincial variation. Interestingly, no cases were reported from the territories.

Figure 6 demonstrates that a higher proportion of CHARGE (A/S) individuals were identified in the

TABLE 15				
CHARGE association/syndrome cases September 1, 2001 to August 31, 2004				
Reported	Duplicates	Excluded	Under review	Confirmed
190	55	32	3	100

**TABLE 16**

**Provincial distribution of confirmed CHARGE association/syndrome cases (n=100)**

	2001	2002	2003	2004	Total
Alberta	1	1	0	7	9
British Columbia	7	2	2	0	11
Manitoba	6	1	2	0	9
Maritimes*	8	5	0	0	13
Newfoundland/Labrador	0	2	0	0	2
Ontario	19	8	5	2	34
Quebec	10	5	0	1	16
Saskatchewan	2	1	3	0	6
Territories†	0	0	0	0	0

\* Maritime provinces include New Brunswick, Nova Scotia and Prince Edward Island.

† Territories include Northwest Territories, Nunavut and Yukon

younger population. Close to 60% of individuals were under six years while less than 20% were 12 years or older.

**Characteristics of the study population**

As demonstrated in Table 17, the frequency of the major and minor features of CHARGE A/S in this study resembled previously published data (Blake et al, 1998; Tellier AL, Report of 47 cases and review, *Am J Med Genet* 1998; 76[9],402-9), with the exception of the characteristic facial features. Interestingly, anomalies that were previously considered to be occasionally or rarely associated with CHARGE A/S were reported with relatively high frequency in this study population. Renal anomalies were noted in close to 40% of individuals. Neck and shoulder anomalies, including a short or webbed neck or sloping shoulders, were noted in 32% of cases. These occasional anomalies might have been considered infrequent findings among individuals with CHARGE A/S because prior studies of CHARGE A/S patients did not specifically ascertain their presence.

**Adolescents and adults**

There were only 19 cases of adolescents and adults with CHARGE A/S identified through the

surveillance. Sixteen cases with complete data are presented in Table 18. Many of these individuals demonstrated the more severe phenotype of CHARGE syndrome. Bilateral posterior choanal atresia, considered one of the more classical features of CHARGE A/S, was present in 7/16 cases (44%), while six individuals had all four major characteristics. Severe feeding problems (14/16) were also common in this older population. Gastroesophageal reflux was reported in 62% (10/16) of individuals and was severe enough to require placement of a gastrostomy tube in 50% (5/10).

Behavioural difficulties, including obsessive-compulsive behaviour, hyperactivity and sleep disturbances were reported in 75% (12/16). Pubertal delay was diagnosed in 67% (8/12) of those who had been assessed.

**Paternal age**

The mean paternal age at the time of birth of individuals with CHARGE syndrome was 31.5 ±5.1 (SD) years (n=54). Among those with all four major

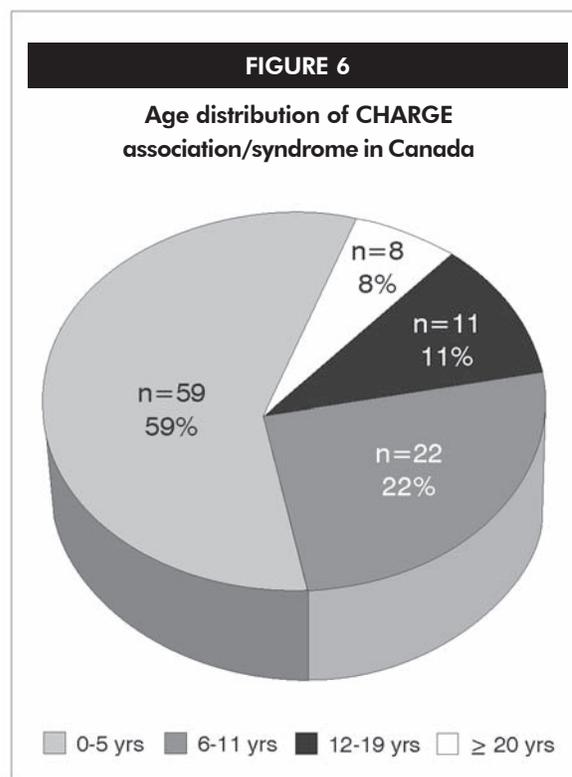


TABLE 17			
Features of CHARGE association/syndrome (n=95*)			
		Number (%)	Blake et al, 1998 (%)
<b>Major clinical criteria</b>	Coloboma	73 (77)	80-90
	Choanal atresia	60 (63)	50-60
	Ear anomalies	94 (99)	90
	Cranial nerves	81 (85)	70-90
<b>Minor clinical criteria</b>	Genital hypoplasia:	37 (39)	N/A
	Males (n=51)	34 (67)	70-80
	Females (n=44)	3 (7)	N/A
	Cardiac malformations	79 (84)	75-85
	Cleft lip/palate	19 (20)	15-20
	TE fistula	19 (20)	15-20
	Characteristic face	52 (55)	70-80
	Growth deficiency	56 (59)	70
<b>Occasional findings</b>	Kidney	37 (39)	15-25
	Hand	15 (16)	rare
	Neck/Shoulder	30 (32)	rare
	Abdomen	11 (12)	15
	Spine	8 (8)	rare

Adapted from Issekutz KA et al, Am J Med Genet 2005;133A:309-17.

\* Although 100 cases have been confirmed, at present, complete data is only available on 95 of those cases.

TABLE 18								
Adolescents and young adults with CHARGE A/S								
	Sex	Coloboma	Choanal atresia	Ear anomalies	Cranial nerve	Feeding difficulties	Behaviour	Endocrine
1	F	Rt Mo	BPCA	Ext, Bil SND	dysfunction*	GER	—	SS, DP
2	F	Bil IC & RC	BPCA	Ext, Mid	Ch, FP	dysph	OC	SS, DP
3	F	Rt Mo	—	Mid, Bil SND	Ch, Sw, V	due to CL/P	HA, OC	SS, DP
4	M	Rt IC, Rt RC	—	—	Ch, V	GER	HA, SI	—
5	F	Bil RC	CA	Ext, Bil SND	Ch, Sw, Bil FP, V	GER, G-tube	—	—
6	M	Bil RC	BPCA	Ext, Mid, Bil SND	Ch, Sw	—	—	SS, DP
7	M	Bil RC	—	Mid	—	GER, G-tube	HA, OC	DP
8	M	Bil RC	—	Ext, Mid, Bil SND	Sw	GER, G-tube	SI, OC	GHD, DP
9	M	Lt IC, Bil Mo	—	Ext, Mid, Bil SND	Ch, Sw, FP, V	Not specified	SI, OC	SS, DP
10	M	—	CA	Ext, Mid, Bil SND	Ch, Sw, V	GER, G-tube, PPD	—	SS, GHD, DP
11	M	Bil RC	—	Ext, Mid, Bil SND	Ch, Sw, V	Not specified	HA, SI	SS, GHD, DP
12	M	Rt IC, Bil RC, Rt Mo	—	Ext, Mid, Bil SND	FP, Sw	GER	HA	SS
13	F	Bil RC, Rt Mo	BPCA	Ext, Mid, Bil SND	Ch, Sw, FP	GER	HA, OC	DP
14	M	—	BPCA	Ext, Mid	Ch, Sw, FP	GER	HA, SI, OC	—
15	F	Bil RC	BPCA	Ext, Mid, Bil SND	FP, V	—	—	SS, GHD, DP
16	F	—	BPCA	Mid	Sw	GER, G-tube	—	SS

Adapted from Issekutz et al, 2005.

Bil: bilateral; BPCA: bilateral posterior choanal atresia; CA: choanal atresia; Ch: chewing problems; CL/P: cleft lip/palate; DP: delayed puberty; dysph: dysphagia; Ext: external ear anomalies; FP: facial palsy; GER: gastroesophageal reflux; GHD: growth hormone deficiency; HA: hyperactivity; IC: coloboma of the iris; Lt: left; Mid: middle ear anomalies; Mo: microphthalmia; OC: obsessive and/or compulsive behaviour; PPD: palatopharyngeal dyskinesia; RC: coloboma of the retina or choroids; Rt: right; SI: sleep problems; SND: sensory neural deafness; SS: short stature (below the 5<sup>th</sup> centile); Sw: swallowing problems and dysphagia; V: vestibular problems.

\* excluding SND

clinical criteria, the mean paternal age was 33.1  $\pm$ 4.9 years (n=17), which is slightly higher than the average paternal age in Nova Scotia of 30.9 years. The mean paternal age among those with three major characteristics or fewer was 30.8  $\pm$ 5.1 years (n=37).

## Conclusions

This surveillance study confirmed 100 CHARGE A/S cases and demonstrated the range of clinical presentation in the Canadian population. It also represents the largest epidemiological cohort in the literature. Certain features, such as neck anomalies, previously thought to be occasionally associated with CHARGE A/S, appear to be relatively common findings. There continues to be provincial variation in confirmed cases suggesting under-reporting in certain regions.

The surveillance identified relatively few adults and adolescents with CHARGE A/S. For a number of these individuals complete data is not yet available. Older individuals with CHARGE A/S face unique challenges, specifically behavioural issues and pubertal delay. In addition, preliminary results of a study on the prevalence of osteoporosis and osteopenia in adolescents and adults with CHARGE A/S suggest a high frequency of osteopenia in this population. Hypogonadism and a decreased level of physical activity relative to controls appear to be contributing factors.

There was a trend toward increased paternal age with increased severity of clinical presentation. However, there was no significant difference in the mean paternal age of the entire study population.

Based on the results of this study, a refinement of the diagnostic clinical criteria was recently proposed (Issekutz KA et al, *Am J Med Genet* 2005; 133A: 309-17) to capture the clinical issues that appear as the child develops, including feeding difficulties, vestibular problems and pubertal delay. This may help to identify older children with CHARGE syndrome. Consistent use of temporal bone imaging

was also recommended as a means to confirm the diagnosis of CHARGE A/S. The discovery of a possible genetic etiology for CHARGE syndrome should facilitate making the diagnosis in the future.

There is much interest in understanding behaviour in individuals with CHARGE A/S. This is an area that will be explored further. A recent study (Smith IM et al, *Am J Med Genet* 2005) gives preliminary results of a cohort of individuals identified through the CPSP surveillance.

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# Congenital rubella syndrome

(January 1996 to December 2004) Final Report

## Highlights

- There was one newborn with CRS reported in 2004 illustrating a missed prevention opportunity.
- From 1996 to 2004, nine of the ten cases were reported to the CPSP, which reinforced routine reporting through Notifiable Diseases Reporting System.
- Canada continues to experience very low incidence of rubella and CRS (0 to 0.6 per 100,000 live births), a reflection of the impact of rubella elimination strategies and the importance of all children receiving their recommended vaccinations.
- Special attention should be given to immigrant women of child-bearing age.
- To prevent missed opportunities, standing orders for vaccination of all rubella-susceptible women in the immediate postpartum period are essential.

## Background

In Canada, rubella immunization programs were introduced in the 1970s. However, the program strategies varied; some provinces initially opted for selective immunization of pre-adolescent females and others opted for immunization of all infants. By 1983, all provinces and territories across Canada had implemented routine measles-mumps-rubella combined vaccine (MMR) at 12 months. During 1996 and 1997, all provinces and territories introduced a routine second dose of MMR or measles-rubella combined vaccine (MR) given at 18 months or four to six years. Some jurisdictions used MR vaccine for their second dose catch-up campaigns.

Since 1970 the incidence of rubella in Canada has declined markedly; fewer than 15 cases were reported

annually in the past two years. During a national consensus conference in 1994, a goal of eliminating indigenous rubella infection during pregnancy by the year 2000 was established. In November 2001, a National Expert Working Group on Rubella recommended that all rubella infections be included in enhanced surveillance, like that of measles. In 2003, the 44<sup>th</sup> Directing Council of the Pan American Health Organization set a goal to eliminate rubella and congenital rubella syndrome (CRS) in the Americas (including Canada) by the year 2010. A national consensus meeting will be held in June 2005 to set specific Canadian immunization goals and objectives for six vaccine preventable diseases (rubella/CRS included) under the National Immunization Strategy.

In Canada, passive reporting of CRS to the Notifiable Diseases Reporting System (NDRS) began in 1979. Active surveillance of CRS began in 1992 through a network of tertiary care paediatric hospitals (now representing more than 90% of paediatric tertiary care beds in Canada) participating in IMPACT (Immunization Monitoring Program, ACTive) and in 1996 through the CPSP.

## Objectives

- 1) To estimate the incidence of congenital rubella syndrome.
- 2) To obtain detailed epidemiological data, including maternal histories, on reported cases of congenital rubella syndrome and infection.

## Case definitions

### Confirmed case

#### Live birth

Two clinically compatible manifestations (any combination from Table 19, columns A and B) with laboratory confirmation of infection:

- isolation of rubella virus from an appropriate clinical specimen; **or**
- detection of rubella-specific IgM in the absence of recent immunization with rubella-containing vaccine; **or**

- rubella-specific IgG persisting at elevated levels for longer than would be expected from passive transfer of maternal antibody, or in the absence of recent immunization.

**Stillbirth**

Two clinically compatible manifestations with isolation of rubella virus from an appropriate clinical specimen.

**Note: The following cannot be classified as a CRS case:**

- rubella antibody titre absent in the infant; **or**
- rubella antibody titre absent in the mother; **or**
- rubella antibody titre declining in the infant consistent with the normal decline after birth of passively transferred maternal antibody.

**Congenital rubella infection**

**Confirmed case**

A case with laboratory confirmation of infection but with no clinically compatible manifestations:

- isolation of rubella virus from an appropriate clinical specimen; **or**
- detection of rubella-specific IgM in the absence of recent immunization with rubella-containing vaccine; **or**
- persistence of rubella-specific IgG at elevated levels for longer than would be expected from passive transfer of maternal antibody, or in the absence of recent immunization.

**Rubella in clinical illness**

**Confirmed case**

Laboratory confirmation of infection in the absence of recent immunization with rubella containing vaccine:

- isolation of rubella virus from an appropriate clinical specimen; **or**
- significant rise in serum rubella IgG antibody levels by any standard serological assay; **or**
- positive serologic test for rubella-specific IgM; **or**
- clinical illness\* in a person who is epidemiologically linked to a laboratory confirmed case.

\* Clinical illness is characterized by fever and rash, and at least one of the following: arthralgia/arthritis, lymphadenopathy, conjunctivitis. Up to 50% of rubella infections are reported to be subclinical.

TABLE 19	
Congenital rubella syndrome: Clinically compatible manifestations	
Column A	Column B
1. Cataracts or congenital glaucoma (either one or both count as one) 2. Congenital heart defect 3. Sensorineural hearing loss 4. Pigmentary retinopathy	1. Purpura 2. Hepatosplenomegaly 3. Microcephaly 4. Microphthalmia 5. Mental retardation 6. Meningoencephalitis 7. Radiolucent bone disease 8. Developmental or late onset conditions, such as diabetes and progressive panencephalitis and any other conditions possibly caused by rubella virus

**Results and discussion**

In 2004, there were eight CRS reports: only one case has been confirmed, three reports were duplicates, three were excluded and one report is missing detailed information (Table 20).

The one confirmed case was a premature newborn female, with intrauterine growth retardation, congenital cataract, microphthalmia, patent ductus arteriosus, pulmonary stenosis, microcephaly, and jaundice. Rubella virus was isolated from the infant’s urine collected on the day of birth, and the serum was positive for rubella specific IgM.

The mother was a G:IV, P:I, A:II, born in South East Asia who immigrated to Canada in the early 1990s. All her pregnancies occurred in Canada: one healthy child, one miscarriage and one interrupted pregnancy. During the most recent pregnancy, the mother visited her home country during the first trimester but does not recall having any symptoms

TABLE 20				
Congenital rubella syndrome cases in 2004				
Reported	Duplicates	Excluded	Under review	Confirmed
8	3	3	1	1

TABLE 21				
Cases of CRS by year of birth reported to CPSP/IMPACT and NDRS from January 1996 to December 2004				
Year of birth	Reported to NDRS only	Reported to CPSP only	Reported to both NDRS* and CPSP	Total
1996	1	0	1	2
1997	0	0	1	1
1998	0	0	1	1
1999	0	0	1	1
2000	0	0	2	2
2001	0	0	0	0
2002*	0	1	1	2
2003*	0	0	0	0
2004*	0	0	1	1
<b>Total</b>	<b>1</b>	<b>1</b>	<b>8</b>	<b>10</b>

\* Notifiable Diseases Reporting System data is provisional.

of rubella infection or having any contact with rubella cases. She was reported to have received rubella-containing vaccine nine years ago, according to her family physician, but documentation is not available as to exactly when and where she received the vaccine. Routine rubella IgG testing before the current pregnancy was not carried out. However, after the current delivery of the CRS infant, stored blood from the mother collected during pregnancy, when tested, revealed the presence of rubella-specific IgM.

During nine years (from January 1996 to December 2004) of active surveillance, ten CRS cases were reported and confirmed in Canada (Table 21). Of the eight cases whose status was recorded, five were born to immigrant women, one to an aboriginal woman, and two to non-aboriginal Canadian-born women. These cases illustrate the need for: a) documented rubella vaccination, b) innovative ways to reach the sub-population of susceptible immigrant women, c) documentation of maternal immunity status by a reliable method, and d) routine practice of postpartum rubella vaccine when indicated.

## Conclusions and recommendations

The very low incidence of CRS and rubella disease suggest that Canada is getting closer to achieving the goal of eliminating indigenous rubella infection during pregnancy. This is in line with the Pan American goal of rubella elimination by 2010. Based on the current incidence pattern, and assuming that the majority of symptomatic rubella cases are detected and reported, it is likely that there is no indigenous transmission of rubella virus in Canada. More epidemiological and virological investigations, including molecular characterizations of rubella virus isolates from Canadian cases, are needed to confirm the status of indigenous virus elimination. Unlike measles, rubella cases could easily be missed because of a lack of clinical specificity and relatively low clinical severity. Whenever possible, clinical specimens should be collected for rubella virus isolation and molecular characterization. The continuing occurrence of CRS involving immigrant mothers, although low, serves as a reminder of the ongoing need to pay special attention to the immunization of this group in order to make sure that CRS prevention opportunities are not missed.

Health-care providers are requested to ensure that:

- All patients receive their rubella vaccinations at the recommended age.
- All women of child-bearing age without documented proof of rubella immunization receive the vaccine. Special attention should be given to women from regions with poor vaccination coverage, including women in immigrant populations.
- All women of child-bearing age have routine rubella antibody screening antenatally by a reliable method. If found to be susceptible, they should be vaccinated in the immediate postpartum period. Standing orders for vaccination of rubella-susceptible women before discharge from hospital is the most effective way to ensure that the opportunity is not missed. This is key to the congenital rubella prevention strategy.

- The recommended 'cold chain' is respected during transportation and storage to avoid vaccine damage and loss of potency.

### Future surveillance

Even though CRS monitoring through the CPSP ended in December 2004, awareness of rubella/CRS among paediatricians and health-care professionals looking after pregnant women must be maintained, and continued surveillance is vital. To this end, enhanced surveillance will continue through other existing surveillance systems: the IMPACT, and provincial and territorial ministries. In addition, it is anticipated that the national enhanced surveillance for measles will be extended to include all rubella/CRS cases, to better understand current epidemiology of the disease, including the role of importation and import-linked cases, chains of transmission, and to formulate appropriate public health strategies to comply with the national and international goals.

### Principal investigator

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## Early-onset eating disorders

(March 2003 to February 2005)

### Highlights

- Ninety-seven percent (97%) of cases were identified in children over eight years of age.
- Food avoidance was the predominant clinical feature.
- Almost half (44%) required an inpatient admission for treatment.

### Background

Epidemiological studies suggest that over the last 50 years the prevalence of anorexia nervosa in young adolescents has been increasing, and it is also suggested that the age of onset of eating disorders is becoming younger. However, there is ongoing debate in the literature about how to apply the current diagnostic criteria for eating disorders to children and younger adolescents. What is known is that significant medical and psychological complications arise from starvation, weight loss or lack of appropriate weight gain during childhood and adolescence making this group of conditions important to recognize and treat appropriately.

This study will document the incidence of early-onset eating disorders (EOED) in Canadian children and provide descriptive data on the abnormal cognitions, behaviours and severity of weight loss or growth failure as a consequence. This otherwise unavailable data will aid in resource allocation and ultimately allow for better understanding and recognition of this condition in younger children where currently the diagnosis may be delayed or missed.

### Objectives

- 1) To determine the minimum estimated incidence of early-onset eating disorders in children and young adolescents aged five to 12 years in Canada.

- 2) To describe the range of medical and psychiatric clinical features at presentation.
- 3) To compare the clinical features in children and young adolescents with existing diagnostic criteria for eating disorders in older patients.
- 4) To describe current therapeutic interventions used in management.

**Case definition**

Any child from five to 12 years of age inclusively, seen in the previous month, with *newly* diagnosed early-onset eating disorder, where *eating disorder* is defined as:

- determined food avoidance and
- weight loss or failure to gain weight during a period of expected growth, not due to any identifiable organic cause such as celiac disease.

**Exclusion criteria**

- Obese children in a supervised weight management program

**Results**

- Estimated incidence is 2.22/100,000
- Male to female ratio is 1:13 (5 boys and 67 girls)
- Mean weight loss is 8.5 kg ( $\pm 5.6$ )

For the diagnosis of an eating disorder in young children between the ages of five and 12 years, the female to male ratio averaged out over the two years to 8:1 (5:1 in year one and 13:1 in year two), as compared to 10:1 in the older adolescent and adult population. Boys are more likely to be affected in the younger age group. The majority of children identified were Caucasian, although Asian and Latin American children were also identified. The group’s mean weight loss was 7.8 kg ( $\pm 5.4$ ) (6.8 kg [ $\pm 4.7$ ] in year one and 8.5 kg [ $\pm 5.68$ ] in year two). This is a substantial weight loss considering that this age group should be gaining weight during these years. The greatest weight loss was found in older children 11 to 12 years of age: girls in this age group lost an average of 9 kg (+6 kg) with a range of 1.4 kg to

TABLE 22				
Early-onset eating disorders cases in 2004				
Reported	Duplicates	Excluded	Under review	Confirmed
93	13	3	5	72

TABLE 23					
Ethnicity					
	Asian	Caucasian	Latin American	Middle Eastern	Unknown
Frequency	3 (4%)	65 (92%)	2 (3%)	1 (1%)	1 (1%)

TABLE 24			
Proportion of children with various symptoms (n=72)			
Symptom	Yes	No	Unknown
Food avoidance	70 (97.2%)	1	1
Excessive exercise	38 (52.8%)	33	1
Self-induced vomiting	9 (12.5%)	57	6
Fear of weight gain or fat	51 (70.8%)	16	5
Perception that body is larger	39 (54.2%)	25	8
Preoccupation with weight	47 (65.3%)	22	3
Preoccupation with food	60 (83.3%)	11	1
Laxative use	0	71	1
Diuretic use	0	71	1
Somatic complaints	24 (33.3%)	46	2
Denial of severity of symptoms	48 (66.7%)	19	5
Smoking	1 (1.4%)	70	1
Weight Loss	56 (77.8%)	15	1

28 kg. This was approximately 18.8% of their total body weight. Boys aged 11 and 12 years old lost an average of 11 kg (+1.41 kg) with a range of 10 kg to 12 kg. This was approximately 21% of their total body weight. Of note is that four of the 63 children (6.5%) for whom data was available failed to gain weight. Almost half (44%) required an inpatient admission for treatment.

<b>TABLE 25</b>			
<b>Co-morbid psychiatric diagnosis (n=72)</b>			
<b>Diagnosis</b>	<b>Yes</b>	<b>No</b>	<b>Unknown</b>
Depression	12 (16.7%)	57	3
Obsessive/compulsive disorder	7 (9.7%)	62	3
Anxiety	17 (23.6%)	50	5
Other	7 (9.7%)	65	0
Psychopharmacologic medication used	12 (16.7%)	51	9
Family psychiatric history	32 (44.4%)	40	0
Change in social situation	39 (54.2%)	30	3

<b>TABLE 26</b>			
<b>Physical effects of disorder (n=72)</b>			
<b>Physical symptom</b>	<b>Yes</b>	<b>No</b>	<b>Unknown</b>
Hypothermia	12 (16.7%)	55	5
Hypotension	18 (25.0%)	53	1
Bradycardia Average beats/minute	26 (36.1%) 35 beats/min	45	1
Admitted to hospital	32 (44.4%)	39	1
Nasogastric tube used	7 (9.7%)	52	13
Patient alive	72	0	0

<b>TABLE 27</b>			
<b>Health-care providers involved (n=72)</b>			
<b>Providers</b>	<b>Yes</b>	<b>No</b>	<b>Unknown</b>
Paediatrician	72 (100%)	0	0
Psychiatrist	37 (51.4%)	26	9
Dietitian	57 (79.2%)	12	3
Psychologist	41 (57.0%)	22	9
Social worker	42 (58.3%)	22	8
Nurse	3 (4.2%)	69	0
Family therapist	7 (9.7%)	65	0
Family physician	1 (1.4%)	71	0

<b>TABLE 28</b>			
<b>Number of children with weight loss by age and sex</b>			
<b>Sex</b>	<b>5-8 years old</b>	<b>9-10 years old</b>	<b>11-12 years old</b>
boys	0	2/3 (67.0%)	2/2 (100%)
girls	1/2 (50%)	8/13 (61.5%)	37/51 (72.5%)

## Conclusion

Paediatricians and psychiatrists are identifying children and younger adolescents with eating disorders. Ninety-seven percent (97%) of cases were identified in children over the age of eight years old. In that group, 80% of the boys (4/5), but only 70% (45/64) of the girls, had lost weight as part of their symptomatology. Averaged out over the two years, 93% of the boys had lost weight while only 75% of the girls were listed as having lost weight. This may indicate that for boys to be identified as having eating problems they have to lose weight, while with girls the eating behaviour may be enough to garner attention. Eating disorders are more common in girls and the community may not be looking for it in boys.

Food avoidance was the predominant clinical feature in all confirmed cases. Many children also displayed a preoccupation with food and weight and a fear of gaining weight. However, like the older adolescent, over half of these children denied their symptoms. Both years of the study identified similar clinical findings.

Finally, one of the criteria for diagnosing anorexia nervosa in females is amenorrhea. Children less than 12 years old would not necessarily be at an age where menarche would have occurred and therefore the criteria of amenorrhea (loss of three consecutive menstrual periods) may not be useful criteria for the diagnosis of anorexia nervosa in children and younger adolescents. Consequently, the majority of the children did not meet the full criteria for anorexia nervosa as outlined in the DSM-IV. This data suggests that it may be difficult to apply the current DSM-IV criteria to children and younger adolescents. There may also be problems in matching clinical populations to the existing classification systems that are based on adults with eating disorders. Developmentally, children have limited ability for insight that would be required to endorse the full spectrum of symptoms.

Furthermore, children and younger adolescents may present with types of clinical eating disturbances

that are different from the classic eating disorders of anorexia nervosa and bulimia nervosa with respect to core psychopathology. Nonetheless, the presenting symptoms are as medically and psychologically problematic.

As seen in the first year of study, some children continued to endorse the symptoms of vomiting (12.5%) and fear of gaining weight (70%). These findings have traditionally been thought to occur in older adolescents and therefore this finding requires further investigation.

The majority of children did not have a history of a comorbid psychiatric diagnosis. However, 44% of this population had positive psychiatric family history. This finding was higher in year two of the study. Fifty-four percent (54%) had changes in their social situation.

Bradycardia was more common in year two at 36% as opposed to 26% and remained the most common medical complication identified. Forty-four percent (44%) of the children were admitted to hospital.

This study is based on a similar data collection undertaken by the Australian Paediatric Surveillance Unit (APSU). After 21 months of surveillance, 45 cases of EOED in Australian children aged five to 13 years (inclusively) have been confirmed. Of the reported cases, 71% are female and 16% are younger than 11 years of age. A decrease in weight in the six months prior to diagnosis was observed in 89% of cases, with a median weight loss of 6 kg.

The profile of clinical features for these identified cases at the time of diagnosis is consistent with those being reported in Canada. However, abnormal medical findings are being reported in a higher proportion of Australian children with temperature less than 35.5°C reported in 40%, and bradycardia (minimum 36 beats/minute) reported in 53% of children. Concurrent depression is also being reported in a higher proportion of Australian children (40%).

Some international variation in management practices may be emerging, with 60% of the Australian sample receiving nasogastric (NG) feeding. This may be a consequence of a slight variation in reporting criteria during the first year of the APSU study, which required only reporting children who were hospitalized. This might explain, in part, why there is a greater proportion of NG feeding reported by the APSU compared to the CPSP study. Surveillance through the APSU will continue until at least 2005.

International comparisons of the data from the EOED studies will enhance our knowledge of this global problem and will contribute to our understanding of early-onset eating disorders throughout the world.

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# Lap-belt syndrome

(September 2003 to August 2005)

## Highlights

- Twenty cases of lap-belt syndrome were confirmed in the first 15 months of the study.
- A third of the victims were less than seven years old; only 15% of the children were adequately restrained.
- Five out of 20 (25%) children were left paraplegic.
- Seat belts save lives, but if worn incorrectly they can cause important abdominal and lumbar spine injuries.
- There is an urgent need for aggressive education efforts to ensure adequate child restraint use in motor vehicles.

## Background

The use of seat belts has clearly reduced fatalities and severity of injuries in motor vehicle crashes. But with the increasing use of seat belts, a new association of injuries has emerged among adults and children involved in motor vehicle crashes. The ‘seat-belt syndrome’ was first described by Garrett and Braunstein in 1962 and refers to injuries to the intestinal viscera and to the lumbar spine associated with seat-belt restraints. Children are especially vulnerable to these injuries, as their intra-abdominal organs are less protected by the thorax and pelvis, they have a lower centre of gravity and their iliac crests are less developed than those of adults, allowing the belt to ride up over the abdomen. To date, there have been very few paediatric studies on the incidence of seat-belt syndrome. In fact, most current knowledge comes from case reports or studies done in limited regional areas. In these studies the number of cases was relatively low, ranging from ten to 50 cases over years.

## Objectives

- 1) Obtain epidemiologic data on the incidence and pattern of injuries encountered in the lap-belt syndrome.
- 2) Identify at-risk age groups.

- 3) Supply data that will help develop new strategies in order to adequately protect children in motor vehicles.
- 4) Promote education and awareness of this rare disease among health-care professionals.

## Case definition

Any child up to and including 18 years of age restrained in a motor vehicle at the time of a crash, with either an abdominal injury, as determined by operation or CT-scan, or thoraco-lumbar spine injuries with or without spinal cord injuries.

## Results and discussion

Twenty children with injuries compatible with lap-belt syndrome were confirmed in Canada between September 2003 and December 2004. Their ages ranged between two and 15 years with a median of eight. Twelve were boys. The average Pediatric Trauma Score was seven (range 3–10). In five crashes, there was a death of another passenger in the car. The median hospital stay was ten days (range 3–155 days) and the median ICU stay was five days (range 0–21 days). Although a third of the victims were less than seven years old, only one was restrained in a booster seat (wearing only a lap belt) and three were properly restrained with a three-point seat belt. Most of them (n=17) were seated in the back and three were passengers seated in the front of a light truck. These results seem to be congruent with a recent published study (Durbin DR et al, *Pediatrics* 2005; 115(3):e305-9). Age-appropriate restraint use is a major protective factor in motor vehicle crashes; only 15% of the children described here were adequately restrained.

Nineteen children had an abdominal lesion. Of these, 13 had an intestinal injury (eight small bowel

TABLE 29				
Lap-belt syndrome cases				
September 1, 2003 to December 31, 2004				
Reported	Duplicates	Excluded	Under review	Confirmed
32	3	7	2	20

perforations only, two small bowel and colon lacerations, one small bowel stricture and two sigmoid lacerations), two had hepatic lesions, four had splenic lacerations, and two had a renal contusion. One patient had a delayed diagnosis of intestinal stricture. Thirteen patients had an abdominal wall ecchymosis or contusion associated with abdominal injury.

Nine patients had lumbar spine fractures (five Chance-type fractures, two compression fractures of a vertebra, one fracture-dislocation of L2-L3 and one comminuted fracture of L2). Five of these patients presented with a complete paraplegia below the level of the lesion and none of these recovered.

With regard to other injuries, no patient had a major head trauma and six patients had thoracic injuries ranging from pulmonary contusion and hemothorax (n=4) to ruptured diaphragm (n=2). Bone fractures other than spinal fractures included pelvis (n=2), sacrum (n=1) and long bone (n=4).

## Conclusion

Lap-belt syndrome can cause severe morbidity, as 25% (five out of 20) of children were left paraplegic. There seemed to be a higher risk for children seated in the front of a light truck. These preliminary results call for high vigilance among physicians for lap belt-associated injuries in restrained paediatric victims, especially if they present with ecchymosis, contusions or abrasions over the abdomen. It also emphasizes the necessity to review restraints in motor vehicles in order to protect children adequately, and the urgent need for aggressive education efforts aimed at adequate child restraint use in motor vehicles.

## Principal investigator

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# Neonatal hyperbilirubinemia – severe

(July 2002 to June 2004) Final Report

## Highlights

- During the two-year study, 259 cases of severe hyperbilirubinemia were confirmed in neonates.
- One hundred seventy-two (74%) cases were readmitted to hospital at a mean age of less than five days of life.
- No etiology was reported in over 70% of cases. Since many of the underlying conditions have serious implications, it is essential to perform adequate laboratory investigations to confirm the etiology.
- Special attention has to be given to early discharged newborns.

## Background

Even though the occurrence of severe neonatal hyperbilirubinemia and bilirubin encephalopathy is very rare, it can be associated with significant morbidity. Bilirubin encephalopathy is a condition that is unfamiliar to most paediatricians practicing today. In the 1940s and 1950s, bilirubin encephalopathy was a common complication of hyperbilirubinemia associated with Rhesus (Rh) disease and occasionally with ABO hemolytic disease. With the introduction of exchange transfusions and Rh immunoglobulin, a reduction in the occurrence of bilirubin encephalopathy was noted. Also, better antenatal monitoring and the availability of intrauterine blood transfusion have eliminated most of the cases of erythroblastosis fetalis, secondary to Rh disease. Phototherapy has drastically reduced the need for exchange transfusions.

In the last several years however, more frequent reports of long-term sequelae in infants with hyperbilirubinemia have been noted (AAP

Statement, 2001; Johnson, 1998). Also, more bilirubin encephalopathy associated with extremely high serum bilirubin levels from infants who appeared to be healthy, breast-fed with no evidence of obvious hemolytic disease (Rh disease or other antibody-related hemolysis) were reported (Penn et al, 1994; MacDonald et al, 1995; Maisels et al, 1995; Harris et al, 2001).

Based on epidemiological studies, a number of risk factors have been found to be associated with severe hyperbilirubinemia in the newborn. These include: jaundice presenting in the first 24 hours, jaundice noted at discharge from the hospital, previous sibling with jaundice, gestational age of 35–38 weeks, breast-feeding, and infant bruising and cephalhematoma (Dennery et al, 2001; Newman et al, 2000). Additional risk factors identified by laboratory investigations include Rh and ABO incompatibility and G6PD deficiency.

The frequency of severe neonatal hyperbilirubinemia during the current era has not been well documented. Attempts to better quantify its frequency, etiologies and associated risk factors in Canada would be of value prior to identifying strategies for risk reduction. Information obtained from a screening program for the detection of glucose 6 phosphate dehydrogenase (G6PD) deficiency or routine determination of blood group and Coombs' analysis on cord blood may help us to achieve risk reduction.

**Objective**

The main objective of the study is to obtain epidemiological data regarding:

- the incidence of severe neonatal hyperbilirubinemia and bilirubin encephalopathy,
- the burden of illness with regards to medical treatment (phototherapy, transfusions and exchange transfusions),
- the neurodevelopmental short-term outcome.

Attempts will be made to identify the timing of presentation of jaundice, etiology and associated triggering or risk factors. This information will help

in the development of prevention strategies (G6PD deficiency screening program, cord blood group and Coombs' test and educational programs).

**Case definition**

Term infants 60 days of age or less with unconjugated hyperbilirubinemia who have had either:

- Peak serum total bilirubin >425 μmol/L or
- Neonatal exchange transfusion

**Exclusion criteria**

Infants who have had exchange transfusion for well-documented Rh isoimmunization disease or are less than 36 weeks gestational age.

**Results**

During the two years of surveillance for severe neonatal hyperbilirubinemia, 367 cases were reported (Table 30). Of these, 259 cases met the criteria for inclusion in this study. Duplication of reporting occurred in 43 cases, 47 cases were discarded and a further 18 did not return the detailed reporting form. The estimated incidence rate was 21.8 cases per 100,000 live births, calculated from a birth cohort of 300,000 per year.

The demographic characteristics of these infants are shown in Table 31. As expected from our inclusion criteria, the mean gestational age was 38.5 weeks with a birth weight of 3,360 g. The average maternal age was 29.8 years. Of the 259 confirmed cases, most were reported from Ontario (n=97), Alberta (n=70) and Quebec (n=42) (Table 32). The vast majority of neonates were readmitted to hospital (74%) and the mean age of presentation was less than five days. As the majority of Canadian women initiate breast-feeding, it is not surprising that nearly

TABLE 30				
Neonatal hyperbilirubinemia—severe cases				
July 1, 2002 to June 30, 2004				
Reported	Duplicates	Excluded	Under review	Confirmed
367	43	65	0	259

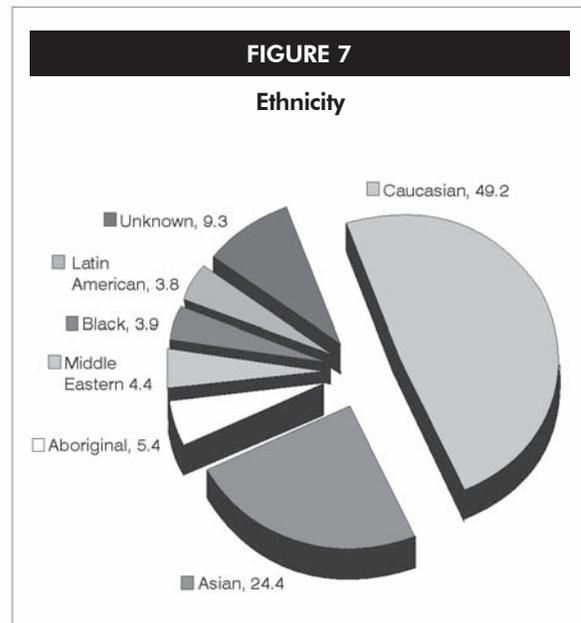
TABLE 31	
Demographics	
Gestational Age	38.5 weeks (36–41)
Birth weight	3,360 g (1,992–5,135)
Age at presentation	4.6 days (birth–19 days)
Feeding practice	81.6% breast-fed
Abnormal neurological signs/symptoms at presentation	20.9%
Readmissions	74.0%

TABLE 32	
Provincial breakdown	
Province	Cases
Alberta	70
British Columbia	24
Manitoba	10
NB, NL	5
Nova Scotia	6
Ontario	97
Quebec	42
Saskatchewan	5
<b>Total</b>	<b>259</b>

TABLE 33	
Diagnosis	
ABO incompatibility	48
G6PD deficiency	20
Other antibodies	12
Spherocytosis	7
Urinary tract infection	2
Sepsis	1
Pyruvate kinase deficiency	1
Hypothyroidism	1
Unstable hemoglobin	1
<b>Total</b>	<b>93</b>

82% of these infants were exclusively breast-fed; 18% were either bottle-fed or received a combination of both. Over 20% had an abnormal neurological examination on presentation that included signs such as hypotonia, decreased responsiveness, abnormal cry and seizures.

The ethnic background of these infants is shown in Figure 7. Only 49.2% of infants with severe



hyperbilirubinemia reported in our study were of Caucasian background. Infants born to parents of other ethnic populations were over-represented in this study, relative to the ethnic makeup of the general Canadian population.

The cause of severe hyperbilirubinemia was identified in about a third of the cases (93 of 259 cases) (Table 33). ABO incompatibility (n=48) was the most common followed by G6PD deficiency (n=20). The diagnosis included: other blood group incompatibility (n=12), spherocytosis (n=7), urinary tract infections (n=2) and sepsis, pyruvate kinase deficiency, unstable hemoglobin and congenital hypothyroidism (n=1 of each). The average peak bilirubin reported was 468  $\mu\text{mol/litre}$ , with a range of 137–773  $\mu\text{mol/litre}$ . The infant with a bilirubin level of 137  $\mu\text{mol/litre}$  required an early exchange transfusion. Phototherapy was required in 99.5% of the neonates for a mean duration of 57.6 hours (4–216). Twenty-two percent (22%) of the neonates had an exchange transfusion. Non-standard treatments included IVIG, albumin and phenobarbital.

### Conclusions

Severe neonatal hyperbilirubinemia continues to occur in term neonates with 74% of reported cases

readmitted at a mean age of 4.6 days for phototherapy (99.5%) and exchange transfusions (22%). ABO incompatibility and G6PD deficiency were identified as important etiological agents in screened infants. In over 70% of reported cases, the underlying etiology could not be identified. It is likely that many of these cases were not completely evaluated at the time of their hospital admission. Since this study relied on voluntary reporting, and not chart reviews, we are unable to always differentiate whether incomplete data reporting was due to incomplete investigation.

These findings highlight the importance of increasing the awareness of physicians responsible for the care of jaundiced neonates. One should perform a complete hematological workup including a CBC, peripheral smear, a screening for maternal and infant blood groups and a Coombs' and G6PD tests. However, in addition to performing an adequate neonatal screening, it seems that evaluation of the condition of jaundiced infants at discharge is of great importance and special attention should be given to breast-fed newborns to prevent readmissions.

Severe neonatal hyperbilirubinemia and its associated long-term neurological sequelae is a potentially preventable disorder. Several of the cases in this study were neurologically abnormal at the time of presentation with hypotonia, decreased responsiveness, abnormal cry and seizures. Although this study was not designed to assess the incidence of long-term neurological disease, such as kernicterus, a subsequent study addressing prevalence of kernicterus and its associated morbidity would be invaluable.

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## Osteogenesis imperfecta

(January 2004 to December 2005)

### Highlights

- Thirteen confirmed cases of osteogenesis imperfecta were reported from Ontario, British Columbia and Newfoundland/Labrador in various ethnic groups.
- The majority (54%) were cases with OI type I, followed by OI IV (23%), III (15%) and II (8%). There were no reports of OI types V, VI or VII.
- One patient was evaluated for physical abuse prior to being diagnosed with OI.
- Nine of the 13 cases are presently receiving treatment with a bisphosphonate agent.

### Background

#### The clinical spectrum of osteogenesis imperfecta

Osteogenesis imperfecta (OI) is a heritable form of osteoporosis that usually presents in childhood. Four different types of OI are commonly distinguished on the basis of clinical features and disease severity, according to the classification proposed by Sillence. Patients with OI type I have a mild phenotype with normal or near-normal height and typically blue sclerae, while OI type II is usually lethal in the perinatal period. OI type III, known as progressive deforming OI, is the most severe form in children surviving the neonatal period. These patients have a characteristic phenotype, including extreme short stature, severe deformity of the spine, thoracic cage and extremities, white or blue sclerae and often a triangular facies. Patients with a moderate to severe form of the disease who do not fit one of the above descriptions are classified with OI type IV; as such, this group is extremely heterogeneous. According to Sillence and to Lubs, patients with the type I phenotype represent 60% of patients with OI, followed by OI type III (20%), type II (10%) and type IV (<10%).

In the majority of cases, OI is inherited as an autosomal dominant trait, though autosomal recessive transmission and gonadal mosaicism have also been described. In about 85% of OI patients, mutations in the genes encoding type I collagen, COL1A1 and COL1A2, can be found. Thus, although collagen type I mutations are frequent in OI, the lack of a detectable mutation does not rule out the diagnosis.

The Sillence classification for OI has recently been expanded by characterizing three additional phenotypes with distinct clinical and histological features (named OI types V, VI and VII). Patients with OI type V demonstrate a striking radiological triad of hypertrophic callus formation, interosseous calcification of the forearm, and a dense metaphyseal band under the growth plate. The inheritance suggests autosomal dominant transmission. Patients with the OI type VI phenotype show subtle distinguishing clinical features, such as normal sclerae and teeth. There is a moderate elevation in alkaline phosphatase levels, as well as characteristic histological features that include increased osteoid thickness and disordered bone lamellation. Despite the mineralization defect at the bone tissue level, there is no evidence for a disorder of mineral metabolism, and mineralization of the growth plate is unaffected. The mode of inheritance in OI type VI is unknown. OI type VII follows autosomal recessive inheritance, recently described in a consanguineous First Nations community from Northern Quebec. Rhizomelia and coxa vara are striking characteristics of the disease, associated with slightly blue sclerae, normal dentition, and moderately severe long bone deformity. This form of OI has been linked to chromosome 3p, outside the type I collagen loci. The precise genetic defect in OI type VII remains to be elucidated.

#### **The changing face of OI: Bisphosphonate therapy**

Frequent fractures and the resulting pain and immobilization are major causes of morbidity among patients with OI. In recent years, the quality of life

for children with severe OI has improved remarkably through the administration of cyclical intravenous pamidronate, in conjunction with multi-disciplinary (surgical and rehabilitative) care. Now that effective treatment is available, prompt diagnosis and initiation of medical and supportive therapy during early life are paramount to enhancing the quality of life for patients with OI. In addition to intravenous pamidronate, studies of other bisphosphonates, including oral agents, are ongoing with the aim to ultimately provide clinicians with a variety of treatment options for patients with OI of differing severities.

#### **The need for current incidence data**

The most reliable estimates of the frequency of OI to date are based upon reports of fractures occurring in the newborn period. However, neonatal fractures are unlikely in OI type I and may or may not occur in OI types III to VII. While the incidence of the disease is estimated to be 1:20,000 to 1:60,000 live births, the true incidence of OI is likely to be much higher. These estimates were established more than 15 years ago, before newer diagnostic techniques (collagen mutation analysis, bone densitometry) became widely available.

## **Objectives**

### **Primary**

To determine the incidence of OI in Canada by ascertaining all newly diagnosed cases over a two-year period.

### **Secondary**

- 1) To raise physician awareness in Canada regarding OI in general and the novel forms in particular, so that diagnoses of OI can be made in a timely fashion, and appropriate treatment can be initiated during the critical years of bone growth and development.
- 2) To identify patients and/or kindreds with novel OI forms (OI types V to VII), for whom the genetic basis is presently unknown, in order to

obtain clinical and genetic information which may ultimately lead to mutation identification.

- 3) To determine whether the OI type VII phenotype, presently only reported in a Northern Quebec First Nations kindred, is present in other First Nations communities or other ethnic groups.
- 4) To determine whether a geographic distribution of OI exists, so that regions in need of a local OI intervention program (including medical, orthopedic and rehabilitative care) can be identified.
- 5) To educate medical health providers and child welfare workers regarding the heterogeneous manifestations of OI, with the aim of facilitating the differentiation of the abused child from the child with congenital bone fragility due to OI. This, in turn, may prevent or minimize false allegations of child abuse.

**Case definition**

**Inclusion criteria**

Any child up to and including 18 years of age with:

- a new diagnosis of OI, defined as a congenital bone fragility condition associated with low bone mass;
- and
- clinical features in keeping with a diagnosis of OI types I to VII (see Table 1 of the protocol).

**Exclusion criteria**

- Bone fragility due to other causes, including genetic disorders (e.g., Ehlers Danlos syndrome), iatrogens (steroids, methotrexate, coumadin, radiotherapy), neuromuscular disease, chronic illness, endocrinopathies, idiopathic juvenile osteoporosis.
- Fractures due to child abuse.

**Results**

In the first year of the study, 41 cases of OI were reported, representing new diagnoses of OI during the study period. Of these, 13 cases have been confirmed (eight girls), with another seven cases presently under review. Twenty-one cases were

TABLE 34				
Osteogenesis imperfecta cases in 2004				
Reported	Duplicates	Excluded	Under review	Confirmed
41	11	10	7	13

discarded, 11 because of duplication of reports and ten because of failure to meet the case definition (Table 34).

**Demographics, ethnicity and OI phenotype**

Of the 13 confirmed OI cases to date, eight were from Ontario. Two other provinces had less than five confirmed cases (BC and NL). The average age at diagnosis was 5.1 years (standard deviation [SD] 5.1; range 0.3–14). Three patients were diagnosed in the first month of life, and one patient was diagnosed antenatally. A summary of ethnicity and OI phenotype are presented in Table 35. The majority of the cases were Caucasian (7/13; 69%). Five patients were of combined ethnicity: First Nations/Caucasian, Asian/Caucasian, Black/Caucasian, Middle Eastern/Caucasian. The distribution of confirmed cases by phenotype was as follows: 7/13 (54%; 4 girls) OI type I, 1/13 (8%; boy) OI type II, 2/13 (15%; 2 girls) OI type III, 3/13 (23%; 2 girls) OI type IV. There were no cases of OI types V, VI or VII reported.

TABLE 35	
Ethnicity and OI phenotype	
	Number of cases
Caucasian	7
Asian	1
First Nations/Caucasian	2
Asian/Caucasian	1
Black/Caucasian	1
Middle Eastern/Caucasian	1
Type I	7 (4 girls)
Type II	1 (boy)
Type III	2 (girls)
Type IV	3 (2 girls)
Types V, VI, VII	0

### Clinical presentation

The mean age at time of first fracture was ten months (SD 11.0; range 0–36). Forty-six percent (46%) (6/13) of cases had sustained five to ten fractures by the time of diagnosis, three cases had sustained more than ten fractures and four reported fewer than five fractures. Only one case had required orthopedic intervention. One of the cases with OI type I, who did not have a family history of OI, had been evaluated for an allegation of physical abuse before the diagnosis of OI was made. Five of 13 cases had a known family history of OI, seven did not, and the information was unavailable in one case. Three cases had undergone type I collagen studies as part of their evaluation, the results of which are pending.

### Therapeutic intervention

Nine of the 13 confirmed cases were receiving bisphosphonate therapy at the time of reporting, three were not being treated medically, and the information was unknown in one case. Eight of the nine treated patients were prescribed intravenous pamidronate; the type of bisphosphonate was not specified in one patient. One of the nine treated cases was participating in an institutional review board-approved (IRB) protocol at the time of reporting; the other treated patients were offered therapy outside of research studies. Four of the nine treated cases had OI type I, the remaining five cases offered medical therapy were diagnosed with OI type II, III or IV. The three patients who were not being treated medically at the time of reporting were those with the mild (OI type I) phenotype.

### Conclusion

In the first 12 months of this study, 13 OI cases of various ethnicities from Ontario, British Columbia and Newfoundland/Labrador were confirmed, the majority of whom manifested the mild OI phenotype (type I), followed by OI types IV, III and II. There were no reports of the more recently described OI phenotypes (OI types V, VI or VII). One of the cases, in which the family history was negative for OI, was evaluated for the possibility of physical abuse before

being diagnosed with congenital bone fragility. Most of the cases, including those with OI type I, were offered treatment with intravenous pamidronate outside of IRB-approved research studies. While pamidronate treatment of moderate and severe OI (types II, III and IV) is generally accepted as standard of care, medical therapy for OI type I is usually recommended only in the context of IRB-approved clinical trials. Whether the OI type I-treated cases manifest more severe type I phenotypes, as is sometimes the case, is presently under review.

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### Acknowledgements

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# Prader-Willi syndrome

(January 2003 to December 2004) Final Report

## Highlights

- In the two-year surveillance study, 35 cases of newly diagnosed PWS were confirmed.
- Sixty-nine percent (69%) of cases were diagnosed before two years of age.
- All PWS cases were confirmed genetically.
- Significant sustained hypotonia in the first year of life associated with feeding difficulties deserve genetic methylation testing.

## Background

Prader-Willi syndrome (PWS) is a rare genetic disorder (abnormality of chromosome 15) with hypothalamic dysfunction leading to hyperphagia and consequent obesity with secondary sequelae of diabetes, heart disease, stroke, sleep apnea, and potential death. Prevalence data in PWS is not well known in Canada but is drawn from estimates on other geographical locales or small population studies. The knowledge of the true Canadian prevalence of PWS will allow for improvements in health-care planning and possible prevention of cardio-respiratory consequences for PWS patients.

## Objectives

- 1) To determine the incidence and the mean age of PWS diagnosis in Canada.
- 2) To ascertain the method of PWS diagnosis: clinical and/or genetic.
- 3) To create an awareness in the scientific community of PWS.

## Case definition

Any child up to and including 18 years of age with newly diagnosed PWS confirmed clinically (PWS clinical score), and/or genetically (methylation and/or FISH [fluorescent *in situ* hybridisation] test). A clinical diagnosis\* of PWS relies on a score derived from major and minor criteria:

- < 3 years: 5 points (4 from major criteria)
- > 3 years: 8 points (5 from major criteria)

\* See [www.cps.ca/english/cpsp/studies/prader.htm](http://www.cps.ca/english/cpsp/studies/prader.htm) for complete clinical scoring

## Results and discussion

During the two-year PWS surveillance study, there were 98 reports. Of these, 53 cases met the inclusion criteria and were confirmed, 35 cases were diagnosed during the study period and 18 before. There were 24 duplicates and ten exclusions. Another 11 reports are under review (Table 36). The Canadian estimated incidence of PWS is predicted at 22 cases per year. The study has so far identified more than three-quarters of the initially estimated number.

Preliminary data from 28 of the 53 confirmed cases included age and clinical features summarized in Table 37. Infantile hypotonia was present in 26, infant feeding problems in 25 and rapid weight gain between one to six years of age in 12 cases.

The PWS diagnosis was confirmed at a mean age of three years in 25 of the 35 cases with available data. However, 69% of cases were confirmed before two years of age. A few patients were diagnosed over the age of nine years; if one excludes this group, as they can skew the real age distribution, the mean age of diagnosis becomes 1.1 year, showing a trend to earlier confirmation of PWS (Table 38).

With the advent and availability of genetic testing for PWS, as well as increased awareness in the medical community, the diagnosis can now be confirmed at an earlier age, allowing for individualized obesity management prevention strategy programming and hopefully better outcome.

TABLE 36				
Prader-Willi syndrome cases January 1, 2003 to December 31, 2004				
Reported	Duplicates	Excluded	Under review	Confirmed
98	24	10	11	53*

\* 35 cases diagnosed during study period and 18 before

<b>TABLE 37</b>			
<b>Clinical features by age of presentation (n=28)</b>			
<b>Clinical features*</b>	<b>&lt;3 years (n=17)</b>	<b>&gt;3 years (n=10)</b>	<b>Adult (n=1)</b>
<b>Major criteria</b>			
Infantile hypotonia	17	9	0
Infantile feeding problems	16	8	1
Rapid weight gain (1–6 yrs)	2	9	1
Facial features	15	10	1
Hypogonadism	5	6	1
Developmental delay	11	9	1
Hyperphagia	2	7	1
<b>Minor criteria</b>			
Decreased fetal movements	15	3	1
Behaviour/Food	1	5	1
Short stature	1	2	1
Sleep problems	0	1	1
Small hands/feet	8	6	1
Straight ulnar border	5	3	0
Hypopigmentation	1	0	0
Esotropia/myopia	1	0	1
Thick saliva	4	0	1
Speech defect	1	6	1
Skin picking	1	4	1

\* The absence of any criteria could be due to: too young an age for developing that feature, improvement as the patient develops, or mild presentation not detected by physician.

All cases were confirmed by genetic testing, with seven deletions, eleven abnormal n-methylation including two maternal uniparental disomy, and another 17 without specific details available.

The incomplete information on genetic testing does not allow for drawing of conclusions related to phenotype/features or clinical presentation.

Ethnicity was reported in 26/35 cases and is the same for the mother and the father in all reported cases. The majority of cases were Caucasian (n=17), followed by Asian (n=6), with the remainder Aboriginal or Middle Eastern. Sixteen cases originated from Ontario, and five other provinces each reported less than five cases (AB, BC, MB, NS, SK).

The preliminary data analysis confirmed the need for a multidisciplinary management approach to the care of these patients since the majority needed interventions in nutrition, occupational therapy, physiotherapy, special education, psychology,

<b>TABLE 38</b>	
<b>Age at PWS diagnosis during the study period, January 2003 to December 2004</b>	
<b>Age at diagnosis of PWS</b>	<b>Mean (range)</b>
Total sample with available age*	3 years (15 days to 14.7 years)
Sample excluding patients over 9 years	1.1 year (15 days to 5.1 years)

\* 25/35: Excludes one adult patient (39 years) diagnosed in 2003 and nine patients without the exact age at diagnosis (six are 12 months or younger and three are respectively around three, five and seven years of age).

endocrinology, ophthalmology, neurology, genetics, gastroenterology, orthopedics and child development. Only two patients were on growth hormone therapy.

## Conclusion

This two-year PWS surveillance study has documented 35 new cases in Canada. All cases were confirmed genetically and although there is a trend to an earlier age at diagnosis (mean age of three years), a few patients were diagnosed over the age of nine years. Physicians should remember that patients presenting with significant sustained hypotonia in the first year of life associated with feeding difficulties deserve genetic methylation testing. One has to reinforce the importance of early detection, diagnosis and multidisciplinary management of PWS-affected children, as the associated obesity is treatable and even preventable in many cases.

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# Severe combined immunodeficiency

(April 2004 to March 2006)

## Highlights

- Five cases of SCID were confirmed.
- All confirmed cases were referred for bone marrow transplant.
- None of the cases thus far were reported in aboriginal children.

## Background

As part of the strategy to reduce the incidence and severity of tuberculosis (TB) in children living on reserves with endemic TB, the First Nations and Inuit Health Branch (FNIHB) of Health Canada recommends the use of the live, attenuated BCG (bacille Calmette-Guérin) vaccine for newborns. Six cases of disseminated BCG infection in First Nations and Inuit children were reported between 1993 and 2002. All six children died, four had severe combined immunodeficiency (SCID), one was HIV positive and one had another immunodeficiency. The observed rate of disseminated BCG in First Nations and Inuit populations in Canada is 205 cases per 1,000,000 doses (CI 42–600), greatly exceeding global estimates of 0.19–1.56 cases per 1,000,000 doses given. While no Canadian data is available on the incidence of SCID, it may well be that this unusual rate of disseminated BCG infection is associated with a high incidence rate of SCID in the Aboriginal population. Hence, data on the incidence of SCID is required to make an evidence-based decision about the risks and benefits of continuing to offer BCG vaccine to First Nations and Inuit children on reserves with endemic TB, and to guide future decisions regarding discontinuation of BCG vaccination.

Severe combined immunodeficiency is a serious, life-threatening condition with high morbidity and mortality. SCID, a group of rare genetic disorders characterized by profound abnormalities in T and B

and natural killer cell development and function, was first reported more than 50 years ago. In the past two decades great advances have been made in the understanding and treatment of SCID. A variety of molecular defects have recently been found to cause SCID, including defects in the gene encoding the common gamma chain (X-linked form), adenosine deaminase deficiency (ADA), interleukin-7 receptor deficiency, janus tyrosine kinase-3 (Jak-3) deficiency and recombinae activating gene (RAG)-1 and RAG-2 deficiency. The two most common forms of SCID are the X-linked SCID (about 50% of all cases) and those due to an ADA deficiency (about 15% to 20%).

General estimates of the incidence of SCID range from 1 in 75,000–100,000 live births with higher than expected rates in Switzerland at 24.3 in 100,000 live births and in the United States Navajo population at 52 in 100,000 live births. No Canadian incidence data for SCID is available.

## Objectives

- 1) To estimate the incidence of SCID in Canada.
- 2) To estimate the incidence of SCID in Aboriginal children in Canada.
- 3) To describe the basic demographics, clinical features and outcomes of SCID in Canada.

## Case definition

Report any child less than two years of age with:

- the clinical features of SCID (i.e., chronic diarrhea, recurrent pneumonia, failure to thrive, persistent thrush, opportunistic infections, etc.)

and at least one of the following:

- an absolute lymphocyte count of less than 3,000/mm<sup>3</sup> or less than 20% CD3<sup>+</sup> T cells
- familial history of primary immunodeficiency.

## Exclusion criteria

Infants with HIV infection or cystic fibrosis.

## Results

Since the study started in April 2004, CPSP participants reported 20 cases of SCID. Of these, nine were duplicates, two were excluded because the cases

TABLE 39				
Severe combined immunodeficiency cases April 1 to December 31, 2004				
Reported	Duplicates	Excluded	Under review	Confirmed
20	9	2	4	5

did not meet the case definition, five cases were confirmed and four cases are awaiting complete detailed case reports and/or confirmation of case status. None of the cases were of Aboriginal descent. Two of the pending cases awaiting further details appear to be infants with pancytopenia who met the case definition for low lymphocyte counts (respectively, 1.160 and 0.950). It may be that the case criteria need to be modified to specifically exclude cases of pancytopenia due to obvious causes (i.e., one case was associated with a cytogenetic defect of monosomy 7).

Of the confirmed cases, there are two females and three males; all were born in Canada and none of the cases report a family history of immunodeficiency. The average age at diagnosis was 5.8 months (range 2–9 months). Confirmed cases include: ADA (adenosine deaminase) deficiency; Omenn's syndrome (awaiting molecular test of RAG gene defect); T–NK+B+ SCID; and T–NK-B+ SCID.

The main clinical features include failure to thrive (80%), interstitial pneumonia (60%), persistent bronchiolitis-like illness (60%), other significant infections (60%) such as septicaemia secondary to *streptococcus viridans*, and other immune related problems (60%) like lymphopenia, neutropenia, eosinophilia, and pancytopenia.

All confirmed cases were referred for bone marrow transplant. Two have received transplants and three are pending. Severe graft-versus-host disease developed in both recipients of bone marrow transplant; one child has died and the other remains severely ill in hospital (six months post-transplant).

## Conclusion

Based on the existing estimates for the rate of SCID and the annual birth rate in Canada, the expected number of new cases of SCID is three to 17 per year. This data indicates that the study is within the range of expected number of new cases. Due to the number of cases still pending, a more detailed analysis of the cases is limited. This study is ongoing until March 2006, at which point a discussion on whether to continue the study based on the number of reported cases will take place.

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# Vitamin D deficiency rickets

(July 2002 to June 2004) Final Report

## Highlights

- During two years of surveillance, 104 cases of vitamin D deficiency rickets were confirmed among children living in Canada.
- The vast majority of confirmed cases were infants and toddlers with intermediate and dark skin, who had been exclusively breast-fed without appropriate vitamin D supplementation.
- The results indicate that rickets remains a major public health problem in Canada and they reinforce the current Canadian Paediatric Society recommendation that exclusively breast-fed infants receive vitamin D supplementation (400 IU/day; 800 IU/day for infants living north of the 55<sup>th</sup> latitude).

## Background

Vitamin D is necessary for calcium homeostasis and for mineralization of the growing skeleton. A deficiency in vitamin D during childhood is associated with potentially significant clinical consequences, as it leads to a mineralization defect of the growth plates (rickets) and of bone tissue (osteomalacia). Poor linear growth and skeletal deformity are hallmarks of vitamin D deficiency during childhood, in addition to hypocalcemic seizures, abnormal dentition, and delayed developmental milestones. The disease is entirely preventable through simple measures, such as ensuring adequate dietary intake of vitamin D or administration of a daily supplement.

Recent literature has proposed that vitamin D deficiency rickets continues to be a public health issue worldwide, and clinical experience suggests that it remains an issue in Canada. This is despite the Canadian regulations requiring that all fluid dairy products (excluding yogurt drinks) be fortified with vitamin D, because infants and children living in Canada cannot depend upon adequate skin exposure to sunlight for vitamin D synthesis. Furthermore, the

Canadian Paediatric Society (CPS) has recommended that all exclusively breast-fed infants receive a daily supplement of oral vitamin D, since breast milk is not a rich source of this nutrient. Despite these preventive measures, vitamin D deficiency rickets appears all too frequently in Canada, with certain geo-ethnic groups continuing to be at heightened risk for developing the disease. The main purpose of this study has been to determine the incidence of vitamin D deficiency rickets among children living in Canada by ascertaining reports of all newly diagnosed cases between July 2002 and June 2004, inclusively.

## Objectives

- 1) To ascertain the incidence of simple vitamin D deficiency (nutritional rickets) among children living in Canada by identifying all newly diagnosed cases over a two-year period.
- 2) To obtain demographic and medical information to determine the profile of children at risk for developing the disease.
- 3) To evaluate the efficacy of current strategies to prevent the development of the disease in Canada.
- 4) To supply data that will assist with the development of novel public health policies to prevent nutritional rickets among children living in Canada.

## Case definition

Children up to and including 18 years of age with calcipenic rickets secondary to simple vitamin D deficiency (also known as nutritional rickets).

### Inclusion criteria

- 1) Low serum 25-hydroxyvitamin D (25OHD)
- 2) Elevated serum alkaline phosphatase

### Exclusion criteria

- 1) Vitamin D deficiency rickets associated with underlying disease, such as fat malabsorption, liver disease and renal insufficiency, and with illnesses necessitating total parenteral nutrition.
- 2) Vitamin D deficiency secondary to heritable disorders of vitamin D metabolism, including:
  - 1 $\alpha$ -hydroxylase deficiency (pseudo-vitamin D deficiency rickets, PDDR)
  - vitamin D receptor defects (hypocalcemic vitamin D resistant rickets, HVDRR).

- 3) Phosphopenic rickets of any etiology (where hypophosphatemia is the primary cause of the rickets, and not due to calcipenic rickets with secondary hyperparathyroidism).

**Results**

Between July 2002 and June 2004, there were 150 reports of vitamin D deficiency rickets among children living in Canada, of which 104 were confirmed cases, 30 were duplicates, 12 were discarded because of failure to meet the inclusion criteria and four are still under review. A summary of the results is presented in Table 40.

**Demographic data**

Case demographic data are presented in Table 41. The majority of confirmed vitamin D deficiency cases (54.8%) were from Ontario, with an additional 13.5% from Quebec, 12.5% from Alberta, and the remaining 19.2% divided among British Columbia, Manitoba, Northwest Territories, Nunavut, Saskatchewan, New Brunswick and Nova Scotia. There were no confirmed cases of rickets from the Yukon, Prince Edward Island or Newfoundland/Labrador. The gender was indicated for 97% of the cases, with 46% being female and 51% male. The mean age at diagnosis was 1.37 years (standard deviations [SD] 0.88; range 0.03–6.34). Twenty-nine percent (29%) of the cases had immigrated to Canada in the months preceding diagnosis. Thirty-three percent (33%) of the confirmed cases were Black, 12.5% were First Nations, 13.5% were Middle Eastern, 11.5% were Inuit, 10.6% were Caucasian, 1% was Latin American and 1% was Asian, while the ancestry was not indicated in the remaining 17.3% of cases. The mean maternal age at the time of delivery was 28 years (SD 6.2; range 15–39).

**Risk factors for vitamin D deficiency**

Eighty-seven and one-half percent (87.5%) of the confirmed cases were classified as intermediate- or

<b>TABLE 41</b>		
<b>Demographics (n=104)</b>		
	<b>N</b>	<b>%</b>
<b>Reporting province or territory</b>		
Ontario	57	54.8
Quebec	14	13.5
Alberta	13	12.5
BC, MB, NB, NS, NT, NU, SK	20	19.2
NL, PE, YT	0	0
<b>Gender</b>		
Male	53	51.0
Female	48	46.2
<b>Recent immigration to Canada</b>	30	28.8
<b>Ethnicity</b>		
Black	34	32.7
Middle Eastern	14	13.5
First Nations	13	12.5
Inuit	12	11.5
Caucasian	11	10.6
Latin American	1	1.0
Asian	1	1.0
Not indicated	18	17.3

dark-skinned. However, fair-skinned children living in Canada were not exempt from developing the disease, as they comprised 10.6% (11/104) of the confirmed cases. Skin colour was not indicated for 1.9% of the cases. Twenty-one of 104 mothers wore a maternal head covering during, and following, pregnancy. Physicians reported that 96.2% of the cases had been breast-fed, three cases were fed infant formula, and the feeding status was not indicated in the remaining confirmed cases. As expected, the vast majority of the cases (86.5%, 90/104) had not received vitamin D supplementation prior to the development of the disease. In the remaining 13.5% of cases, supplementation with vitamin D was either not indicated on the case report form or was unreliably administered by caregivers prior to diagnosis. Only 12.5% of mothers were documented as having received vitamin D supplementation during pregnancy. Following delivery, this number fell to 4.8%, and the majority of mothers did not drink milk in the post-natal period. Milk allergies and sunscreen use did not appear to be significant risk factors for vitamin D deficiency among children in Canada, as only six of the confirmed cases manifested a milk allergy, while frequent sunscreen use was documented in only two of the cases.

<b>TABLE 40</b>				
<b>Vitamin D deficiency rickets cases</b>				
<b>July 1, 2002 to June 30, 2004</b>				
<b>Reported</b>	<b>Duplicates</b>	<b>Excluded</b>	<b>Under review</b>	<b>Confirmed</b>
150	30	12	4	104

### Clinical and biochemical features at diagnosis

The most frequent signs and symptoms at diagnosis included: skeletal deformity (44.7%), seizures (15.4%), failure to thrive (10.6%), fractures (9.8%) and delayed milestones (5.7%). The remaining 13.8% of cases presented with an incidental discovery of rickets (i.e., identification of a rachitic thoracic cage at the time of x-ray for a respiratory infection). Twenty-five percent (25%) of patients presented with a combination of these signs and symptoms. Analysis of the serum biochemical parameters of bone and mineral metabolism prior to initiation of vitamin D therapy revealed a mean alkaline phosphatase level of 1,237 U/L (range 186–6,067). A 25-hydroxyvitamin D level prior to treatment was available in 78 of the 104 confirmed cases, with a mean value of 21.4 nmol/L (SD 16.7; range 1–84). A total calcium level prior to treatment was available in 83 of the 104 confirmed cases, giving a mean value of 1.94 mmol/L (SD 0.43; range 1.07–2.60).

### Conclusions

Over the two years of this surveillance study, 104 cases of nutritional rickets were confirmed among children, predominantly infants and toddlers, residing in Canada. Intermediate- and dark-skinned children who were breast-fed without appropriate vitamin D supplementation were at greatest risk for developing the disease, although fair-skinned children were not exempt from the disease. A proportion of the mothers were veiled, and most did not receive vitamin D supplementation following delivery, nor did they ingest milk (thus eliminating a potential dietary source of vitamin D). Significant morbidity was present at diagnosis in most of the confirmed cases, including limb deformity, seizures, failure to thrive, fractures and delayed developmental milestones.

While breast milk should continue to be advocated as the ideal nutritional source for infants and children, it must be recognized that breast milk is not a rich source of vitamin D. This becomes particularly relevant for infants living in northern countries such as Canada. In view of our northern latitude, it has been recommended by the CPS since 1998 that all exclusively breast-fed infants receive supplementation with oral vitamin D (400 IU/day; 800 IU/day for infants living north of the 55<sup>th</sup> latitude). However, the results of this study

highlight that the CPS position statement regarding vitamin D supplementation has not reached its full audience, and as such has not been universally implemented by health-care providers. Though it is not surprising that children with the greatest number of risk factors for vitamin D deficiency were the most frequently diagnosed, it is surprising that this condition is being detected in a country with ready access to vitamin D supplementation and a clear recommendation from the country's national paediatric organization for prevention of the disease.

Given the potential for significant morbidity associated with rickets, there is an urgent need for heightened awareness among health-care providers and the general public to prevent the condition. Studies to evaluate the success of educational interventions are a reasonable next step. Consideration should also be given to the role of financial barriers in ensuring that vitamin D is administered to all breast-fed infants in Canada. Alternate modes of vitamin D therapy to ensure adequate stores during breast-feeding, such as antenatal treatment of vitamin D-deficient mothers, are worthy of future investigations. Finally, the potential role of vitamin D deficiency in the development of serious childhood and adult illnesses, including type I diabetes, bone fragility and multiple sclerosis, remains an important area of current study.

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### Acknowledgement

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# New Studies in 2005

## Congenital cytomegalovirus infection

(March 2005 to February 2007)

*“Torch the TORCH screen for congenital CMV diagnosis.”*

Congenital cytomegalovirus infection (CMV) is the commonest congenital infection affecting from 0.2% to 2.4% of all live births. Approximately 10% of infected infants exhibit significant clinical illness in the newborn period with a variety of manifestations, including poor growth, microcephaly, jaundice, hepatosplenomegaly, anemia and thrombocytopenia. Almost all of these infants will go on to have later neurologic sequelae. Even if asymptomatic at birth, approximately 5% to 17% will have neurodevelopmental abnormalities, including sensorineural hearing loss, which may only become apparent in infancy or later in childhood. Congenital CMV infection is a difficult diagnosis to prove retrospectively, as definite diagnosis requires isolation of the virus from the newborn in the first three weeks of life. Diagnosis beyond that age may indicate acquired infection from exposure to virus in the birth canal or breast milk. Newborns often do not produce specific IgM after early fetal infection so a “TORCH screen” is a poor way of making the diagnosis.

This infection has devastating consequences and is of great public health significance. Active surveillance for congenital CMV infection is timely as intervention strategies are on the horizon. Careful follow-up of infected infants should be an integral part of a universal newborn hearing screening program, antiviral therapy is showing promise and vaccines are in active development.

This study will gather Canadian data on identified cases of congenital CMV infection. This surveillance affords two unique opportunities for external validation. There will be simultaneous laboratory-based surveillance of diagnostic virology labs in Canada to validate case ascertainment by the CPSP. Comparisons will also be made between results of similar surveillance done by the Australian and British surveillance units.

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## Congenital myotonic dystrophy

(March 2005 to February 2008)

*“Although the genetic and pathophysiological aspects of CMD are rapidly being discovered, epidemiology and clinical knowledge are still largely based on anecdotal experience.”*

Myotonic dystrophy is a multisystem disorder characterized primarily by muscle weakness and myotonia commonly beginning in early adulthood. Two loci for the disease are known and described as

DM1 and DM2. At both loci inheritance is autosomal dominant with DM1 associated with a CTG trinucleotide expansion on chromosome 19q13 and DM2 with a CCTG tetranucleotide expansion at 3q21. The primary pathogenesis is felt to be related to the effect of large accumulations of mutant mRNA in the nucleus of cells.

In DM1 only, a more severe clinical phenotype and earlier age of onset can occur over subsequent generations, as the unstable trinucleotide repeat carried by the parent, almost always the mother, can expand further during gametogenesis. This phenomenon is known as genetic anticipation and, in this context, leads eventually to an infant with congenital myotonic dystrophy (CMD). Although there can be a wide spectrum of symptomatology, the child often has evidence of hypotonia, weakness, feeding difficulties and mechanical respiratory failure requiring intubation and ventilation immediately after birth.

Although the genetic and pathophysiological aspects of CMD are rapidly being discovered, epidemiology and clinical knowledge are still largely based on anecdotal experience. For example, the relationship between genotype and phenotype remains unclear and the decisions related to cases of children requiring prolonged neonatal ventilation are not consistent. This study has chosen a broad definition of CMD to gather information on the full spectrum of morbidity and health resources needed for children with signs and symptoms of myotonic dystrophy in the newborn period. As the genetic confirmation of the disorder typically requires several weeks, much valuable clinical information will be known to the reporting paediatrician by the time the diagnosis is confirmed. In addition, a cohort study will be undertaken, outside the CPSP, with consenting families to understand long-term clinical outcomes.

Because CMD is rare the CPSP is the ideal mechanism to ascertain a population-based profile

of the epidemiology and neonatal characteristics of this unique genetic disorder.

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## Head injury secondary to suspected child maltreatment (abuse or neglect)

(March 2005 to February 2007)

*“Although rare, cases of inflicted head injury are of great clinical importance, as a large proportion of them result in permanent neurological deficits.”*

Despite the fact that the term ‘battered child syndrome’ was first used in 1962, the study of child maltreatment is still in its infancy in Canada. This is true even though maltreatment comprises a major cause of mortality and morbidity for Canadian children and youth. The literature on the incidence of child maltreatment in Canada is limited to two main studies. The Canadian Incidence of Reported Child Abuse and Neglect study found that in 1998,

2.1% of children were investigated for maltreatment, and abuse was substantiated in nearly a half of these cases. This is likely an underestimate of the true incidence as many cases of child abuse are not reported.

The second study was a recently published ten-year chart review of 364 cases of shaken baby syndrome (SBS) treated at 11 Canadian paediatric centres. This study excluded cases of inflicted injury that did not involve evidence of shaking and included only hospital cases of SBS, thereby limiting the generalisability of its findings. One quarter of the cases presented with non-specific signs, and 40% had no sign of external injury, making the diagnosis difficult and highly dependent on the physician's awareness of the possibility of child abuse. Several studies have shown that physicians feel unprepared and have inadequate knowledge to deal with cases of abuse and neglect. In 2001, only three of 16 Canadian paediatric academic centres reported mandatory clinical training in child protection for paediatric residents.

Although rare, cases of inflicted head injury are of great clinical importance, as a large proportion of them result in permanent neurological deficits; 19% of the children in the SBS study died and 75% had an impairment at the time of hospital discharge. As a result there is much support for tracking these injuries.

Thus, the purpose of this study is to conduct active surveillance for head injury secondary to suspected maltreatment in Canadian children. In order to document as completely as possible the presenting picture, the study will include children and youth up to 14 years of age.

The investigators hope that this study will raise awareness among physicians, better define the clinical presentation, document the patterns of presentation and the burden of illness, and direct strategies for primary, secondary and tertiary prevention of these serious injuries.

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## Medium-chain acyl-coenzyme A dehydrogenase deficiency

(September 2005 to August 2007)

*"Active surveillance of MCAD deficiency is timely as it will allow for comparison between provinces with and without universal newborn screening."*

Fatty acid oxidation disorders are a common cause of unrecognized morbidity and mortality in childhood. Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency is the most frequent inherited fatty acid oxidation disorder with an incidence of about 1 in 10,000–20,000. Although the disease can occur at any time in life, the commonest presentation is between three months to two years.

Usually, a relatively well child decompensates during an acute illness associated with vomiting and develops hypoglycemia, mild hepatomegaly and altered sensorium. Other biochemical features include hypoketosis, mild hyperammonemia and elevation in liver enzymes. If unrecognized, the clinical picture can worsen with seizures, coma, residual neurological deficits and subsequent developmental delay. At the initial presentation, the mortality risk is as high as 25%.

The inheritance of MCAD deficiency is autosomal recessive. Prognosis is excellent once the diagnosis is made and treatment initiated early thus making a strong argument for newborn screening.

MCAD deficiency still remains underdiagnosed and there is very little incidence data for the Canadian population. With the advent of tandem mass spectrometry, neonatal screening for MCAD deficiency is now occurring in four provinces (BC, SK, NS, PE).

Active surveillance of MCAD deficiency is timely as it will allow for comparison between provinces with and without universal newborn screening. This study will provide data on incidence, burden of illness and clinical outcome, which might guide public health policy in terms of advocating for universal newborn screening for MCAD deficiency.

### Principal investigator

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## Survey Question

### Acquired demyelinating syndromes of the central nervous system

(February 2004)

The incidence of acquired demyelination of the central nervous system in Canadian children is unknown. Children experiencing acquired demyelination face an uncertain future, as a small proportion will go on to experience recurrent demyelinating attacks that characterize Multiple Sclerosis (MS).

The Paediatric Demyelinating Disease Network initiated a survey to determine the number of children in Canada experiencing acquired demyelination and to determine the proportion of those children who were subsequently diagnosed with MS. The study also inquired whether MS was considered by the treating physician.

The survey was sent out to 2,320 paediatricians and paediatric subspecialists across Canada. Results of the 611 responses (26%) indicated that 130 (21%) had cared for a child with acquired demyelination within the last two years. A total of 285 patients were reported. Each paediatrician had seen from one to 60 patients, with an average of 2.3 per paediatrician. Six of the 130 respondents did not indicate the number of patients they had assessed. Forty-six of the 285 patients with demyelination (16.14%) experienced recurrent demyelinating episodes and were subsequently diagnosed with MS.

Paediatricians were asked whether the possibility of recurrent demyelination was entertained, as many health-care professionals may not consider MS as a possible diagnosis of an initial demyelinating event. Eighty-four of the 130 paediatricians (65%) who have seen a case indicated that they considered MS

as a possible outcome of acute demyelination in children.

The CPSP Steering Committee has since approved a full two-year study on acquired demyelinating syndromes of the CNS that began in April 2004. To date, 52 patients with acute demyelination have been reported. Study results are found on page 15. A follow-up survey will be sent out at study completion to assess whether a greater proportion of paediatricians are considering MS as a potential outcome in patients experiencing a first demyelinating episode.

Demyelination in Canada may not be as rare as previously thought. It is hoped that the study will successfully assess the incidence and clinical features of paediatric demyelination in Canada as well as increase awareness among paediatricians of paediatric MS as an outcome of demyelination. The advent of disease-modifying therapies for MS and the recent evidence of improved long-term outcome associated with early therapy initiation emphasize the need for prompt diagnosis and coordinated care for children affected with MS.

#### Principal investigator

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*\* Representing the Pediatric Demyelinating Disease Network (22 paediatric care facilities across Canada)*

### Acute flaccid paralysis

(November 2004)

As part of a Public Health Agency of Canada study to explore practices relating to the investigation of acute flaccid paralysis (AFP) cases in Canada, a one-time survey was included in the November 1, 2004, CPSP mailing to 2,378 paediatricians participating

in the program. The survey aimed to establish background rates of paediatrician clinical encounters with acute flaccid paralysis cases and to explore their most recent experiences with follow-up laboratory investigations for stool testing.

A total of 628 paediatricians responded by mail and an additional 13 respondents participated in an online version of the survey posted on the CPS web page. The overall response rate was 27% (641/2,378).

Of those who participated in the survey, 463/641 (72%) reported that they would collect stool cultures within 14 days of onset of paralysis, which is the WHO recommended time frame for collection of viable stool specimens for isolation of polioviruses.

As expected, AFP is a rare condition and only 51/641 (8%) participating paediatricians reported having seen a case in the previous two years. Of these, 21/51 (41%) paediatricians reported ordering stool cultures for isolation of polioviruses. Thirteen (62%) of the 21 who ordered stool cultures reported receiving results from the laboratory, while the remaining six (28%) reported unknown or unsatisfactory results.

Of the 26 who did not order stool cultures (26/51), the main reasons specified fell into the following categories: patient referred to a specialist/paediatric neurologist (8/26); clinical presentation or other tests preferred over stool testing (7/26); patient presented too late for stool testing (1/26); not specified (10/26).

## Discussion and next steps

The results from this survey are consistent with AFP surveillance data. From 1993 to 2003, surveillance data indicate that while less than 50% of AFP cases had stool collected for isolation of polioviruses, over 90% had one or more neurological investigation conducted. Given that over 90% of AFP cases in Canada are diagnosed as either Guillain-Barré syndrome or transverse myelitis, clinical signs and symptoms consistent with these conditions may

favour neurological investigation and thereby pre-empt polio-specific investigations. Though only three AFP cases were diagnosed as having had an acute infectious process (due to non-polio enterovirus infections) during the last decade, all of three had polio-specific stool and/or serologic investigations completed.

Findings from the one-time survey together with the analysis of ten years of surveillance data indicate that while the majority of paediatricians are aware of the recommended time frame for polio specific stool collection, the WHO surveillance target of stool collection for  $\geq 80\%$  of AFP cases is not being met and deficiencies exist in laboratory follow-up and feedback of results.

The polio eradication project has been one of the greatest public health challenges in history. Despite global efforts, the disease remains endemic in six countries in Africa and Asia and threatens to re-establish transmission in several neighbouring countries. Countries and continents certified as polio-free remain at risk of wild virus importation from endemic areas. Increasing globalization underscores this risk. Therefore, reliable and effective surveillance systems continue to be vital for detecting possible importation of wild and vaccine-derived poliovirus.

While Canada remains committed to global polio eradication efforts through active surveillance of AFP, surveillance data indicate that key targets of surveillance system performance are not being met. Feasibility and appropriateness of alternate surveillance indicators should be explored for Canada where specialized diagnostic investigations are more readily available. To this end, a more detailed survey of paediatric neurologists is planned to fully explore and quantify reasons why viral stool cultures are not regularly requested. The goal of this follow-up survey is to summarize current practices in AFP surveillance in Canada and to consider the potential for alternate criteria for AFP surveillance indicators.

## Principal survey investigator

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## Infant bath seats

(June 2004)

The Consumer Product Safety Bureau of Health Canada had become aware of an infant drowning hazard linked to the use of infant bath seats and bath rings. Accordingly, Health Canada made use of the Canadian Paediatric Surveillance Program to obtain a better understanding of the frequency and extent of injuries, near-miss drownings and drownings associated with infant bath seats and bath rings in Canada. This was accomplished by surveying the experience of Canadian paediatricians treating such incidents, both in hospitals and private practices. The results stated in this summary represent one of a number of sources of data Health Canada has collected concerning incidents involving the use of infant bath seats and bath rings.

The survey question was designed to focus on infants as they are considered the target group for use of these products. The expected age range for the use of this product is from six to nine months, representing the time frame in which an infant can sit unassisted, to when they can pull to a standing position. However, several incidents reported to Health Canada have involved infants outside this age range.

A total of 1,087 paediatricians returned the survey, representing an overall return rate of 47.1%. Of the returned forms, 25 were received from paediatricians

who recalled caring for one or more infants who had experienced injuries, near-miss drownings, or drownings related to the use of an infant bath seat or bath ring in the last two years. Seven paediatricians indicated that they would not have seen this type of incident due to the nature of their work.

In all, 2.3% of respondents reported treating one or more injuries, near-miss drownings, or drownings related to the use of infant bath seats and bath rings during the last two years. The breakdown of the data indicated that respondents treated a minimum of 34 infants with incidents including: 20 injuries (scrapes, cuts, bruises), 12 near-miss drownings, and two deaths.

Many of the paediatricians included comments on the returned survey. Nine noted lack of supervision, not the product itself, as the problem; four commented that these were dangerous devices and should be removed from the market; three were not aware that these types of products existed; three added that they frequently receive questions from parents about these products; and two indicated they used these products themselves for their children.

## Conclusions

The findings of this survey offer a profile of the experience of Canadian paediatricians in treating, in the last two years, injuries, near-miss drownings, and drownings associated with infant bath seats or bath rings.

The Consumer Product Safety Bureau of Health Canada has received reports of nine injuries, 19 near-miss drownings, and 11 drowning deaths linked to the use of infant bath seats and bath rings since 1983. However, of these reported incidents, one injury, six near-miss drownings, and nine deaths have occurred in the last five years. In the United States, the Consumer Product Safety Commission has received reports of 163 injuries or near-miss drownings and 106 deaths due to the use of these products from January 1983 through October 2003. The Canadian Paediatric Surveillance Program

survey indicated that among paediatricians who responded to this survey, 2.3% have treated one or more infants for injuries, near-miss drownings, or drownings in the last two years.

Typically, drownings linked to bath seats and bath rings occur as a result of the infant bath seat becoming unstable and tipping over in the bath, the infant climbing out of the infant bath seat, or the infant slipping through the leg opening and become lodged under water. Despite clear warning labels stating *Prevent drowning. Never leave child unattended* on the older bath seat models and *Prevent drowning. Always keep baby within arm's reach* on the newer models, in the majority of incidents, the infant had been left unattended or under the supervision of a sibling.

In the months ahead, Health Canada will review options to consider the public health implications of the survey findings. In addition, an advisory and a public education bulletin will be issued and posted on the Consumer Product Safety website: [www.hc-sc.gc.ca/hecs-sesc/cps/index.htm](http://www.hc-sc.gc.ca/hecs-sesc/cps/index.htm)

### Principal survey investigator

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## ADR Tips of the Month

In January 2004 a study on serious and life-threatening adverse drug reactions (ADRs) was added to the CPSP to better understand the incidence and nature of ADRs in children. Study results are found on page 24. To build both support for and awareness of the study, in addition to providing a mechanism for the dissemination of new drug safety information, 'ADR Tips of the Month' was launched. The tips, sent on a monthly basis with the initial reporting form, have been developed with a short, simple and consistent format. Information conveyed has ranged from specific drug safety warnings relevant to the treatment of children, such as SSRI (selective serotonin reuptake inhibitors), fentanyl, lamotrigine, oseltamivir phosphate, and over-the-counter medications, to general reminders for the completion of data elements on detailed reporting forms. To allow for wider dissemination of the information, all tips are posted on the CPSP website.

To establish the level of support for this new awareness strategy, a simple survey was sent to CPSP participants in November 2004. Results suggest that the 'Tips of the Month' are relevant and effective at meeting the needs and interests of the participants. Seventy-nine percent (79%) of respondents indicated that they read the tips and of these respondents, 77% found them useful. Numerous comments and suggestions were provided supporting the short, simple format. The practical nature of the messages conveyed was viewed positively.

### Principal investigator

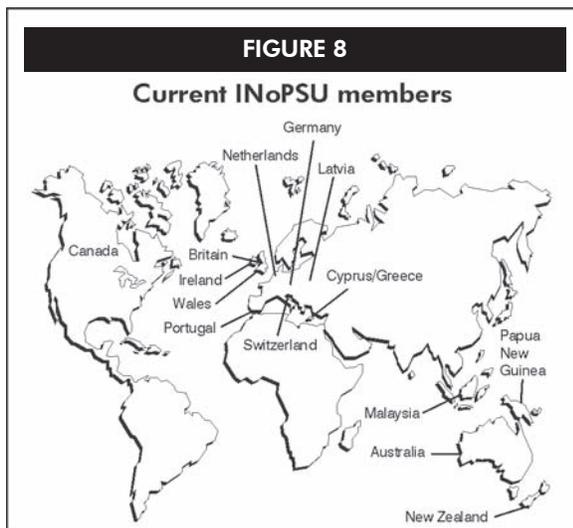
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# International Developments

**INoPSU** The International Network of Paediatric Surveillance Units

(INoPSU), established in 1998, continues to enhance collaboration between national paediatric surveillance units. INoPSU provides a unique opportunity for simultaneous cross-sectional studies of rare diseases in populations with diverse geographic and ethnic characteristics.

Currently worldwide, there are 13 national paediatric surveillance units that are full members of INoPSU: Australia, Britain, Canada, Germany, Ireland, Latvia, Malaysia, Netherlands, New Zealand, Papua New Guinea, Portugal, Switzerland, and Wales. The Cyprus/Greece surveillance unit is an affiliate member until such time as it fulfills the requirements of full membership. As well, the British Ophthalmological Surveillance Unit is an associate member. In 2004 Trinidad and Tobago also became an associate member. Argentina is currently developing a surveillance unit.



The first formal INoPSU meeting was held in Ottawa in June 2000, with a second meeting in York, England, in April 2002. As a result of these successes, a third INoPSU meeting was held in Portugal in the spring of 2004. The fourth INoPSU conference will be hosted by the BPSU in London, England, in the spring of 2006.

## INoPSU collaboration in action

### 24<sup>th</sup> International Congress of Paediatrics

Dr. Elizabeth Elliot from Australia and Dr. Danielle Grenier and Andrea Medaglia from Canada represented INoPSU at the International Paediatric Association conference in Cancun, Mexico, August 15-20, 2004. The symposium session presented collaborative INoPSU research possibilities and achievements through various examples. The session was well received and created both discussion and interest, in particular, from Argentinean, Mexican and Venezuelan delegates. Time will tell whether or not more North and South American countries will join INoPSU but from initial interactions, prospects look promising.

### Argentina

Following in the footsteps of the British Paediatric Surveillance Unit, who helped Canada, Portugal, and Trinidad and Tobago's respective units get off to a good start, CPSP representatives had the opportunity and privilege to work with Argentinean colleagues as they were creating a Perinatal Network in Buenos Aires City and ten Buenos Aires Provinces and sought guidance on integrating and implementing an active surveillance system for neonatal-perinatal problems.

A collaborative program held in Buenos Aires in July 2004 included interactive workshops on the nuts

and bolts of establishing and running an active surveillance program as well as neonatal study results to illustrate the versatility and potential of this epidemiological tool.

This collaborative endeavour was most enlightening and enriching for all. The Argentinean Paediatric Society and program

participants are committed to integrating active surveillance into their Perinatal Network Project and are currently selecting their first research studies and determining future priorities. The CPSP looks forward to continued collaboration and has encouraged the Argentinean Network to establish links with INoPSU and apply for membership in 2006.

<b>TABLE 42</b>	
<b>Studies under surveillance by national paediatric surveillance units in 2004</b>	
<b>Study</b>	<b>National paediatric surveillance units</b>
Abdominal injury due to child abuse	BPSU
Acquired demyelinating syndromes of the central nervous system	CPSP
Acute encephalitis	PPSU
Acute flaccid paralysis	APSU, CPSP, NZPSU, SPSU
Acute rheumatic fever	CPSP, SPSU
Adverse drug reactions – serious and life-threatening	BPSU, CPSP
Adverse effects from complementary and alternative medicine	APSU, WPSU
Alcohol and children	IPSU
Anaphylaxis following food ingestion	APSU
Ataxia	NSCK
Atypical mycobacterial infections	ESPED
Atypical tuberculous infection	NSCK
Autism in children under 5 years	IPSU
CHARGE association/syndrome	CPSP
Childhood conversion disorder	APSU
Chronic interstitial lung disease	ESPED
Complicated pneumonia including empyema	WPSU
Congenital cytomegalovirus infection	APSU, BPSU, CPSP (approved 2004)
Congenital malformation after maternal use of epileptics	NSCK
Congenital myotonic dystrophy	CPSP (approved 2004)
Congenital rubella syndrome	APSU, BPSU, CPSP, NZPSU, SPSU
Congenital toxoplasmosis	BPSU
Diabetes mellitus	ESPED, IPSU, LPSU, PPSU
Down’s syndrome	NSCK
Early-onset eating disorders	APSU, BPSU, CPSP
Fetal alcohol syndrome	APSU
Foregut and hindgut malformations	NZPSU
Fragile X	IPSU
Head injury secondary to suspected child maltreatment (abuse or neglect)	CPSP (approved 2004)
Hemoglobinopathy	NSCK
Hemolytic-uremic syndrome	LPSU, NZPSU, PPSU, SPSU
Henoch-Schönlein purpura	NSCK
Hepatitis C virus infection	APSU, CPSP
Hereditary periodic fever syndrome	ESPED
HIV/AIDS	APSU, BPSU, LPSU, NSCK, NZPSU
Hodgkin’s lymphoma	LPSU
Hypernatremia	NSCK
Hypocalcemic salt-losing tubulopathies (inherited)/Bartter-like syndromes	ESPED
Idiopathic thrombocytopenic purpura	NSCK
Inborn errors of metabolism	NZPSU

C P S P 2 0 0 4 R E S U L T S

Influenza infections (fatal/near fatal)	ESPED
Ingestion of lamp oil (intoxications)	ESPED
Insufficient breast-feeding	NSCK
Intussusception	SPSU
Invasive fungal infections in VLBW infants	BPSU
Invasive group B streptococcus	ESPED, PPSU
Invasive <i>Haemophilus influenzae</i> infections (all types)	ESPED
Juvenile idiopathic arthritis	WPSU
Kawasaki disease	CGPSU, PPSU
Langerhans cell histiocytosis	BPSU
Lap-belt syndrome	CPSP
Leukemia	LPSU
Malaria	NSCK
Measles (complications)	ESPED
Medium-chain acyl-CoA dehydrogenase deficiency	BPSU, NSCK, CPSP (approved 2004)
Meningoencephalitis	PPSU
Munchausen by proxy syndrome	APSU
Neonatal herpes simplex virus infection	APSU, BPSU, SPSU
Neonatal hyperbilirubinemia–severe/kernicterus	BPSU, CPSP, ESPED
Neonatal sinus venous thrombosis	ESPED
Nephrotic syndrome (idiopathic)	NSCK, NZPSU
Nesidioblastosis	LPSU
Neural tube defects	SPSU
Non-Hodgkin's lymphoma	LPSU
Non-type 1 diabetes	BPSU
Opsoclonus myoclonus syndrome	IPSU
Osteogenesis imperfecta	CPSP
Pancytopenia	CGPSU
Pertussis	CGPSU
Pneumococcal sepsis/meningitis	ESPED, NZPSU
Prader-Willi syndrome	CPSP
Progressive intellectual and neurological deterioration	BPSU
Prolonged infantile cholestasis	NZPSU
Respiratory syncytial virus (RSV) disease	SPSU
Reft syndrome	APSU
Septo-optic dysplasia	WPSU
Severe combined immunodeficiency	CPSP
Shaken baby syndrome/Subdural haemorrhage (<2 years)	NSCK, SPSU, WPSU
Small bowel insufficiency	NSCK
Splenectomy and hyposplenism	WPSU
Systemic lupus erythematosus	ESPED
Thrombocytopenia	IPSU
Thrombosis (neonatal sinus venous)	BPSU, ESPED
Thyrotoxicosis	BPSU
Tick-borne encephalitis	SPSU
Tuberculosis	BPSU, WPSU
Varicella/zoster infection	BPSU, ESPED, SPSU
Vitamin D deficiency rickets	CGSPU, CPSP
Vitamin K deficiency bleeding/HDNB	APSU, BPSU, NZPSU
West syndrome	CGPSU

**Legend:**

APSU	Australian Paediatric Surveillance Unit	MPSU	Malaysian Paediatric Surveillance Unit
BPSU	British Paediatric Surveillance Unit	NSCK	Netherlands Paediatric Surveillance Unit
CGPSU	Cyprus/Greece Paediatric Surveillance Unit	NZPSU	New Zealand Paediatric Surveillance Unit
CPSP	Canadian Paediatric Surveillance Program	PNGPSU	Papua New Guinea Paediatric Surveillance Unit
ESPED	German Paediatric Surveillance Unit	PPSU	Portuguese Paediatric Surveillance Unit
IPSU	Irish Paediatric Surveillance Unit	SPSU	Swiss Paediatric Surveillance Unit
LPSU	Latvian Paediatric Surveillance Unit	WPSU	Welsh Paediatric Surveillance Unit

## Highlights from other national paediatric surveillance units

### Australia

The use of complementary and alternative medicine (CAM) is widespread in Australia. Like any other treatment, CAM has the potential for causing adverse events. The study conducted through the Australia Paediatric Surveillance Unit is the first systematic study in Australian children of adverse events due to CAM. Several areas of particular concern have been identified:

- Significant dangers associated with dietary restriction including dehydration and malnutrition (resulting in one death).
- Potential risks of CAM use in pregnancy.
- Potential risks from overdose of CAM and the need for safe storage/child resistant packaging. In one child, ingestion of an herbal remedy for vomiting resulted in acute hepatic toxicity requiring liver transplantation.
- Dangers associated with substituting conventional medication with CAM. In one child, substitution of a CAM for an anti-epileptic agent resulted in life-threatening seizures.

Clinicians need to ask about CAM use and be prepared to discuss potential benefits and risks involved.

### Britain

The BPSU major achievement of the past year was securing five years of funding from the Department of Health. The Royal College of Paediatric and Child Health established the Sir Peter Tizard bursary for paediatricians to undertake an epidemiological study using the BPSU. The first bursary was awarded for a study on childhood thyrotoxicosis and a second bursary will be looking at paediatric malaria. Two new studies involved expanding the list of participants:

the study on non-type 1 diabetes added the active surveillance of diabetic nurse specialists, and the study of early-onset eating disorders in children less than 13 years will involve the active surveillance of child and adolescent psychiatrists.

Another important endeavour was the production of two brochures: a public information leaflet on BPSU activities and an introduction to the BPSU program infrastructure, aims and achievements for dissemination to researchers enquiring about the process of undertaking a new study.

### Cyprus/Greece

Research projects conducted from April 2002 to December 2004 by the Cyprus/Greece Paediatric Surveillance Unit included West syndrome, Kawasaki disease, pertussis, pancytopenia and vitamin D deficiency rickets.

### Germany

Vaccine failures related to the use of Hib vaccines in the Netherlands and in UK reported in 1993 caused a lot of concern regarding the efficacy of Hib vaccines, particularly when given in combination with DTPa. Combined vaccines have been used in Germany since 1996, and ESPED data demonstrated a constantly low rate of infections. Most of the cases were in unvaccinated or incompletely vaccinated children. A recent publication has demonstrated an excellent long-term efficacy of tetra- and pentavalent combination vaccines, including Hib, in Germany (Kalies H, Verstraeten T, Grote V, Meyer N, Siedler A, Schmitt HJ, Breuer T, Moulton LH, von Kries, R, Erhebungseinheit-fur-seltene-padiatrische-Erkrankungen-in-Deutschland-Study-Group. Four and one-half-year follow-up of the effectiveness of diphtheria-tetanus toxoids-acellular pertussis/*Haemophilus influenzae* type b and diphtheria-tetanus toxoids-acellular pertussis-inactivated poliovirus/*H. influenzae* type b combination vaccines in Germany. *Pediatr Infect Dis J* 23 [2004]944-50).

## Ireland

Preliminary 2003 data of the study on alcohol and children identified 59 children who presented to hospital with events relating to alcohol ingestion. The median age was 14 years, 60% were female and 88% required admission. Spirits (72%) and beer (22%) were the most common drinks taken. Alcohol levels were alarmingly high with a mean of 216 and a range of 112 to 380 mg per dL. This study highlighted the importance of alcohol in adolescence. It also demonstrated the relatively poor IPSU returns at 75% and even lower completion of validation questionnaire. More intensive surveillance in one area suggested that the problem was much greater than our figures would suggest. Alcohol experimentation and excessive ingestion among adolescents merit greater paediatric scrutiny.

## Latvia

Latvia continues active surveillance in the areas of haematology/oncology, endocrinology, nephrology and HIV/AIDS.

## Malaysia

Established in December 1993, the Malaysian Paediatric Surveillance Unit began surveillance in September 1994 reaching around 400 paediatricians and surgeons. Initially there were four conditions under surveillance: paediatric HIV/AIDS, neonatal meningitis, acute fulminating liver failure and death from asthma. Duchenne muscular dystrophy was added in 1998 and neonatal congenital heart disease in 1999.

## Netherlands

The surveillance study on Down syndrome aimed to measure quality of life aspects and use of Down syndrome teams. There were 222 and 189 reported cases in 2003 and 2004 respectively. Age at diagnosis was 1.8 days when born in hospital (71.5%) compared to 16.1 days when born at home (28.5%). After birth, hospital admission

for diagnosis and treatment occurred in 84.6% of cases, most often unnecessarily. The mean age of the mothers was 33.5 years. Paediatricians (83%) used the Down protocol of the Dutch paediatric association. One or more cardiac defects were found in 54.6% of reported children and 40% had audiology screening, 34% of these were positive. A follow-up study is planned.

## New Zealand

The national study of bronchiectasis in children less than 15 years of age found the incidence to be 3.7 per 100,000, over seven times higher than the only other national study undertaken in Finland. This means bronchiectasis is nearly twice the incidence of cystic fibrosis. The disease occurred unevenly among the childhood population. In particular, children of Pacific ethnicity had more than ten times the rate than children of European ethnicity. While the mean age of diagnosis was five years, most had had symptoms for more than two years by the time they were diagnosed.

The importance of this study is that it clearly illustrates the significant presence of what is often a preventable childhood condition that can have sequelae throughout life. There is a need for greater vigilance for its early manifestations, so the diagnosis is made and appropriate care can be initiated.

## Portugal

Early results of a four-year study on group B streptococcal neonatal infection (<90 days of age) conducted by the Portuguese Paediatric Surveillance Unit led to new guidelines by the General Health Directorate that now recommends universal screening of all pregnant women in their third trimester. Further study results have already shown a significant decline in the incidence of this condition during the last year of surveillance. The unit concluded surveillance of this condition in March 2005.

TABLE 43	
Tick-borne encephalitis study	
Clinical picture	Number (%)
Total cases	60 (100)
Not hospitalized:	22 (37)
<6 years	6 (27)
Hospitalized:	38 (63)
<6 years	6 (16)
Diagnosis:	
meningitis	18 (47)
meningoencephalitis	20 (53)
myelitis/radiculitis	0
Sequelae (upon discharge):	
none	25 (66)
minor	8 (21)
moderate	2 (5)
severe	3 (8)

### Switzerland

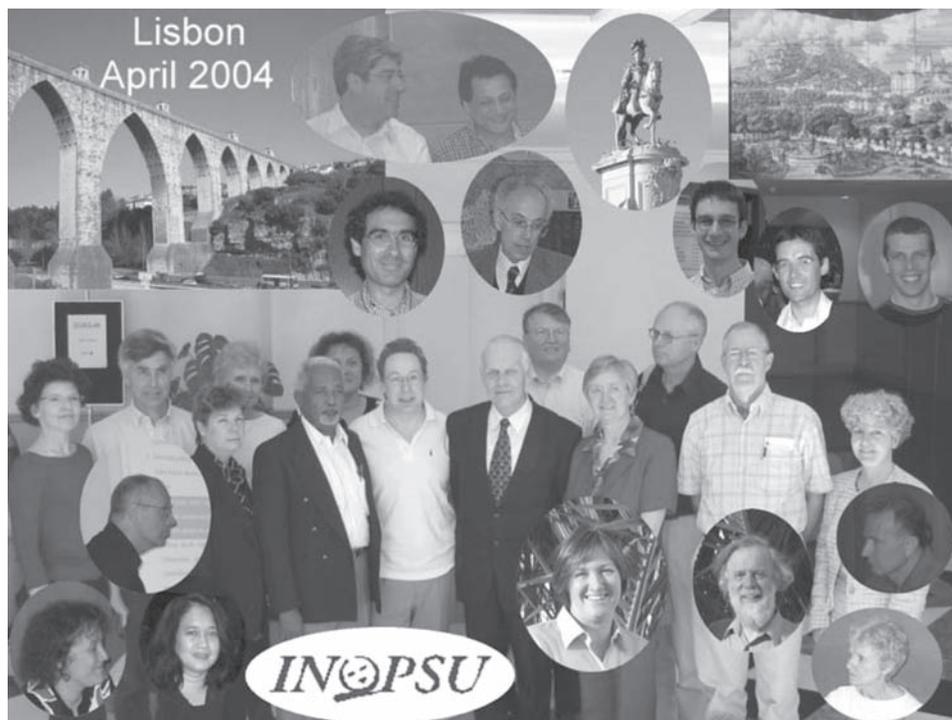
Between March 2000 and February 2003, the tick-borne encephalitis (TBE) study documented 60 confirmed cases. Reports from SPSU have been periodically compared and completed with notifications from the Swiss Federal Office of Public Health. The results represent the data from both sources.

The clinical picture is shown in Table 43. The incidence of hospitalizations for children 6–15 years of age is equal to that of adults. TBE is rare in

children less than six years of age. It is not clear if this is due to reduced exposure or to reduced risk of disease after exposure in this age group. These results nonetheless give support to the current immunization recommendations in Switzerland where in most cases vaccination against TBE is not indicated in children less than six years of age.

### Trinidad and Tobago

The Trinidad and Tobago Paediatric Surveillance Unit is currently seeking funding and once surveillance commences in 2005, a study on the vertical transmission of HIV/AIDS will be considered. The unit will provide reliable and useful information on important childhood disorders, thereby facilitating child health-care delivery systems. Moreover, it is expected that this unit shall help graduate students as well as other investigators to conduct relevant clinical epidemiological research.



# Call for New Studies

## Research opportunities

### Wanted

- Investigators to initiate new CPSP studies on childhood disorders that are high in disability, morbidity, mortality and economic costs to society, despite their low frequency.
- The paediatric community to take up the challenge of proposing a wide range of research studies.
- Interested individuals prepared to assume a leadership role in developing protocols and analyzing study data.

### The tool

#### The CPSP is:

- A well-established, timely, cost-effective surveillance infrastructure.
- A multi-faceted surveillance tool capable of collecting reliable data in a variety of different fields.
- An effective means of monitoring low-frequency, high-impact diseases and conditions.

### Track record

- An 82% overall initial response from more than 2,400 paediatricians.
- An impressive 96% data completion rate for the 608 cases reported in 2004.
- High duplicate reporting rate (16.8%) assuring case ascertainment and participant commitment.

### International flavour

- Be part of INoPSU (International Network of Paediatric Surveillance Units) a growing network of national paediatric surveillance units that exists in 13 countries around the world.
- Take advantage of international collaboration, as INoPSU studies provide a remarkable opportunity to compare similar data and learn more about rare diseases worldwide.

### Looking for ideas?

Here are a few examples of studies suggested through the program evaluation survey:

- |  |  |
|--|--|
| • Biliary atresia                                    | • Brachial plexus injury                 |
| • Bronchiectasis                                     | • Childhood tuberculosis                 |
| • Circumcision complications                         | • Complementary and alternative medicine |
| • Complications of body piercing                     | • Congenital parvovirus B19 infection    |
| • Congenital varicella                               | • Familial melanoma                      |
| • Heavy metal poisoning                              | • Herpes zoster in children              |
| • Histiocytosis disorders                            | • Imported malaria                       |
| • Invasive Group B streptococcus in neonates         | • Laryngeal papillomatosis               |
| • Methicillin-resistant <i>staphylococcus aureus</i> | • Neonatal <i>Listeria</i> infections    |
| • Non-type 1 obesity-related diabetes                | • Kawasaki disease                       |
| • Severe hypernatremia                               | • Severe iron deficiency in preschoolers |
| • Sudden death in asthma                             | • Type 1 diabetes                        |

The potential for new studies in different paediatric subspecialties is endless. If you have a research project in mind, please contact the CPSP Senior Coordinator at 613-526-9397, ext. 239, for more information.

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