

Report in Focus

IMPROVING MEDICINES FOR CHILDREN IN CANADA

Children who are ill need treatment that is appropriate for their age and stage of development. Yet surprisingly medicines are regularly administered to infants, children, and youth without full knowledge of their safety and efficacy in those groups, particularly among younger children, in intensive care settings, and for certain drug classes (e.g., antidepressants). Any use of a medicine that departs from what is approved by the regulator, such as using a medication for an unapproved condition or age — referred to as off-label use — creates the potential for harm since the drug may not be effective or it may cause serious unexpected side-effects. Without drug safety and efficacy studies in children, these potential harms remain unknown.

The view that children should only be included in research as a last resort has shifted in recent years. Regulators, medical professionals, and health researchers now believe that children's participation is important to reduce inequities in health and improve the evidence base to inform better health care. In response to this paradigm shift, policies have evolved to allow regulators, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), to require studies with children, and provide incentives for such research. Canada is in a position to align with this approach and direction and to improve medicines for children of this generation and generations to come. *Improving Medicines for Children in Canada* offers insights into the opportunities and challenges that exist for our country and provides the evidence required to establish a path forward.



CHARGE TO THE EXPERT PANEL

Recognizing the importance of developing safe and effective medicines for children in Canada, the Minister of Health, on behalf of Health Canada, asked the Council of Canadian Academies (the Council) to respond to the following question:

What is the state of clinical pharmacology, in Canada and abroad, that can be applied to the ethical development of safe and effective pharmaceuticals and biologics labelled as therapies for infants, children, and youth?

In response, the Council assembled an international, multidisciplinary panel of 14 experts (the Panel). The Panel examined peer-reviewed academic literature, publicly available government reports, and other literature relating to research involving children. In addition, the Panel commissioned an original analysis of prescription drug use in children. The final report focuses on the ethical development of safe and effective medicines for children; examines gaps in the current state of knowledge on the relationships among clinical pharmacology, human development, and pediatric drug investigations; and identifies opportunities for strengthening knowledge of safe and effective pediatric medicines.

“Improved research that targets children will be an important step in improving health outcomes and strengthening the evidence base that informs medical practice.”

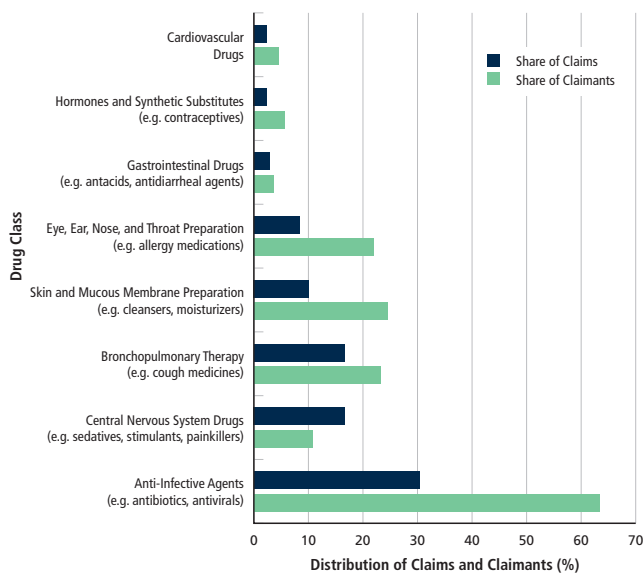
– Stuart MacLeod, Chair, Expert Panel

Key Findings

The Panel identified five key findings that serve to answer the charge put forward by Health Canada:

1. Children take medications, many of which have not been proven safe and effective for their use.

Each year, about half of Canada’s seven million children use at least one prescription medicine, and prescriptions in children less than one year old are even higher. The Panel found that for children under age 13, antibiotics represent the most commonly prescribed drug class, followed by central nervous system drugs, which can be used to treat conditions such as attention deficit hyperactivity disorder, pain, seizures, autism spectrum disorder, and schizophrenia (see Figure 1). Examples of commonly prescribed drugs are listed in Table 1.



Data Source: IMS Health Canada Incorporated Private Pay Direct Drug Plan database (2013)

Figure 1

Types of Medicines Commonly Used by Children, 2012

This figure lists some of the types of medicines most commonly used by children under the age of 13 years. It indicates the classes of drugs that represent a majority of use in 2012. Share of claimants adds to more than 100% as claimants may have submitted for coverage of drugs from more than one category.

Table 1. Top Drugs by Share of Claims, 2012*

| Drug | Share of Claims (%) |
|------------------------|---------------------|
| Amoxicillin | 14.5 |
| Methylphenidate HCl | 7.4 |
| Salbutamol | 6.9 |
| Fluticasone Propionate | 5.8 |
| Clarithromycin | 4.0 |
| Azithromycin | 3.3 |
| Cefprozil | 2.5 |
| Montelukast Sodium | 2.4 |
| Mometasone Furoate | 2.3 |
| Hydrocortisone Acetate | 2.1 |

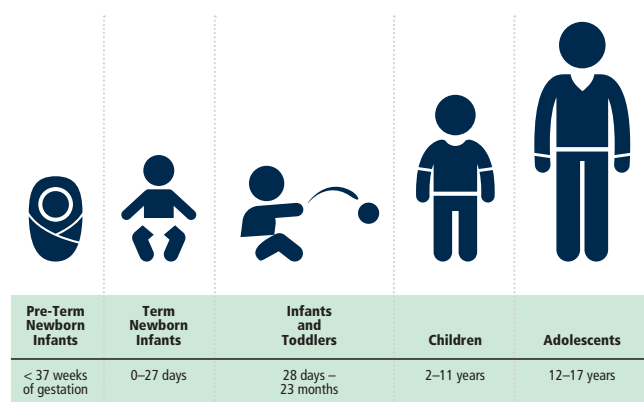
Data Source: IMS Health Canada Incorporated Private Pay Direct Drug Plan database (2013)

Children’s need for medicines is clear. Yet few drugs available in Canada are approved for their use. As a result, most drugs given to children are used off-label, without regulatory review of information about safety and efficacy and without appropriate dosages, forms, or formulations. In the absence of a validated and comprehensive authority, clinicians are often required to use other sources, including hospital formularies and online drug information resources. The Panel identified an opportunity for Canada to develop a consolidated source of up-to-date, pediatric-specific evidence to inform and improve consistency and accuracy in real-world use of medicines for all age groups. They noted the value of a comprehensive national prescribing resource that includes pediatric information, such as those that exist in the United Kingdom, the Netherlands, and Australia.

2. Children respond to medications differently from adults; thus, medicines must be studied in children and formulated for children.

As children grow, they experience significant developmental changes that impact how their bodies deal with medications and how medications in turn affect their bodies. Thus, drug responses vary not only between children and adults, but also among different stages of development (see Figure 2).

The most dramatic age-related physiological changes occur during the first year of life. Responses can also vary due to a number of factors unrelated to age and development. These include genetic make-up, concurrent therapies, disease state, diet, environment, and many others. In some cases, the combination of developmental, genetic, and other factors may result in serious adverse drug reactions.



Data Source: ICH (2000)

Figure 2
Five Stages of Human Development

The ICH has established a range of categories that mark stages of human development (ICH, 2000). Using age divisions such as these, researchers have been able to demonstrate that drug responses vary not only between children and adults, but also among children of different ages and stages of development. Standardization of age groups and other study parameters such as outcome measures can help to improve consistency and comparability of drug studies.

A medication's *form* (e.g., tablet or liquid) and *formulation* (i.e., the combination of medicinal and non-medicinal ingredients) may affect a number of variables, including: how a child's body processes it; the medication's overall safety and efficacy; and the degree to which the child will accept and adhere to the prescription regimen. Often, forms designed for adults are manipulated or tailored for children. This can increase the risk of dosing error. The best scenario for treatment involves commercially available age-appropriate forms and formulations. In the absence of such options, detailed, standardized, and evidence-based recipes for manipulating formulations would improve drug safety and efficacy. The design and prescribing of pediatric medicines, from birth through to adolescence, would benefit from considering these broad factors (e.g., developmental stage, genetic make-up, form and formulation) and their interactions.

3. Studying medicines in children is always possible and is in their best interests.

Consistent with current international thinking, many within Canada's health research community are embracing the idea that children should be protected *through* research, not *from* research. Today, a range of methods and designs are increasingly accepted as ethically and scientifically sound. The appropriateness of different methodologies varies based on the study objectives and available evidence, but demonstrating safety and efficacy of a medicine in studies with children is always feasible and desirable.

The randomized controlled trial (RCT) is a common and trusted approach for testing drug efficacy and in most cases is possible for children. However, flexibility in medicines research with children is important. Table 2 notes some pediatric-specific challenges of efficacy trials and some potential approaches for overcoming them. These approaches are detailed in Chapter 5 of the report.

Table 2. Challenges and Potential Approaches for Pediatric Efficacy Studies

| Pediatric-Specific Challenge | Potential Approach |
|---|--|
| There is a lack of pediatric-specific information to answer questions about precise study design parameters. | Create study designs that allow for planned interim adjustments and modifications (e.g., changes to sample size) based on accumulating data. |
| There is hesitancy to enroll children in drug studies because of amplified ethical and perceived acceptability concerns (e.g., possible assignment to placebo group). | Create designs that decrease the time spent on placebo or ensure that all patients eventually receive treatment. |
| There are fewer children to enroll in drug studies compared to adult populations. | Create study designs that pool resources (e.g., multi-centre studies) or study individual patients. Use analysis techniques that maximize existing data (e.g., extrapolation). |
| Traditional techniques for collecting and analyzing blood samples may not be appropriate for small children. | Use alternatives to blood (e.g., saliva) or use residual blood drawn for medical care. Incorporate analysis techniques that use low sample volumes and/or measure multiple drugs in one sample. |

“Children should be protected through research, rather than from it. Ultimately, children deserve treatment appropriate for their age and for their stage of development.”

– Stuart MacLeod, Chair, Expert Panel

The frequent lack of pre-marketing trials in children and consequent off-label use effectively means that drug safety in children is often assessed *only* in the post-marketing setting. Rare or unexpected adverse drug reactions (ADRs) are also often detected only by post-marketing collection and analysis of safety data. Thus, high-quality post-marketing safety studies are critical for children. Decisions about pediatric drug safety may be supported by well-designed ADR databases that encourage and simplify reporting of all suspected ADRs (even those that result from off-label use) and enable retrieval of pediatric-specific data. For children, it is particularly important to ensure that ADRs that affect physical or psychological development are investigated using long-term follow-up studies. Taking advantage of analysis techniques and surveillance initiatives that better detect or predict ADRs could also support improved knowledge of drug safety and effectiveness in children. In particular, evidence suggests that there may be greater benefit in active surveillance initiatives over more passive surveillance techniques.

4. In the United States and the European Union, pediatric medicines research is encouraged, required, and monitored in ways that offer lessons for Canada.

Currently, Health Canada can request, but has no authority to compel, a manufacturer to submit pediatric data or apply for a pediatric indication (i.e., an approved use in children). Additionally, a regulatory incentive for manufacturers to submit data on pediatric use of drugs in Canada has had limited success. This is an area where Canada could learn from the experiences of other regulators in creating policy options to benefit children’s health. To encourage pediatric drug research, Health Canada’s counterparts in the United States (the FDA) and the European Union (the EMA) have used a combination of:

- **Regulatory authority:** Regulators have authority to require drug manufacturers to carry out pediatric study;
- **Incentives:** Drug manufacturers are offered incentives in return for safety and efficacy studies; and
- **Infrastructure:** Supporting activities such as collective priority setting, platforms that allow sharing of information, and encouraging communication and partnership between academia, clinical settings, industry, and regulators are cultivated.

As a result, manufacturers submit pediatric safety and efficacy data to regulators in these countries. Often these same data could be used for regulatory review in Canada. Nevertheless, any policy solution must recognize the unique Canadian context, the strengths and limitations of current regulatory options, and the need for a tailored response.

5. Pediatric medicines research is a Canadian strength, but it requires reinforcement and sustained capacity and infrastructure to realize its full potential.

One of Canada’s strengths is the capacity among patients, families, care providers, researchers, regulators, industry experts, ethicists, and funders to collaborate through research. Many of the resources required for collaboration among these groups are already in place, in technical and clinical expertise, training facilities, research networks, and database infrastructure.

Canada also has a proven track record in pediatric clinical trials and drug safety monitoring:

- Researchers at several well-respected Canadian children’s hospitals have led high-quality and high-profile international studies, such as the Caffeine for Apnea of Prematurity (CAP) study led out of McMaster University;
- Researchers are beginning to harness the study potential of available population and health service databases by linking and analyzing pediatric-specific information contained in different databases (e.g., efforts in Saskatchewan and Manitoba);
- Various networks for drug research have been established in Canada, such as the Maternal Infant Child and Youth Research Network, allowing for more efficient planning and carrying out of clinical trials; and
- Canadians lead or support international pediatric research initiatives, such as the respected Standards for Research in Child Health collaboration.

Although a unified effort has not yet been defined, there are opportunities to reinforce pediatric medicines research in Canada and internationally. Several of these opportunities are discussed in Box 1.



BOX 1: Key Opportunities for Reinforcing Pediatric Medicines Research in Canada

Coordinated Research Agenda: Large-scale, coordinated efforts that identify key research priorities hold significant promise with regards to the development of new and better treatment options for children. These efforts could include (1) supporting multi-centre studies and research networks that build a diverse set of evidence and leverage research strengths across jurisdictions; and (2) encouraging the synthesis of evidence to maximize the use of information and reduce duplication in future research.

Standardization: Initiatives that are working to develop standards, combine efforts, and provide tools, guidance, and infrastructure for pediatric trials will help to support ethical, consistent, and meaningful drug studies in children. For example, standardizing age ranges and outcome measures will make studies relevant and enable comparisons between trials investigating the same drug. In addition, harmonizing ethical norms for research involving children, including those related to emerging issues (e.g., genetic testing), will clarify the research process. Institutional cooperation for processes such as ethics review of research proposals could also expedite clinical trials.

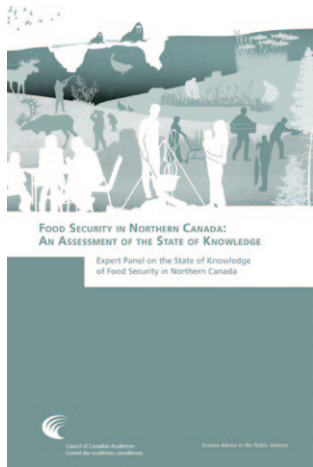
Communication: Researchers and regulators can encourage open dialogue on study designs that are feasible for investigators and acceptable for regulatory approval of drugs for pediatric use. Regulators can then build on that shared understanding by providing guidance on situations for which alternative designs may be accepted. Furthermore, open communication with patients or families on concepts such as developing relevant outcome measures in clinical trials would help contribute to a culture shift among the public that encourages research.

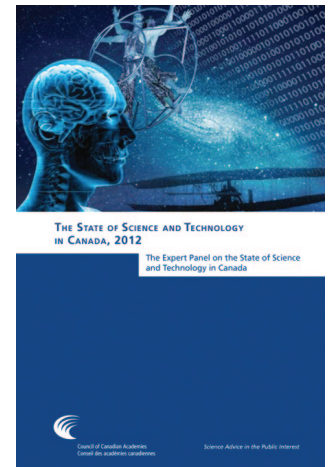
CONCLUSION

Scientific studies both inform regulatory decisions and are the basis of the practice of medicine. A lack of scientific evidence for clinical use can expose a patient to unnecessary risk of harm; for some aspects of pediatric medicines, the unknowns are many. There is a clear opportunity for Canada to improve the health and safety of the millions of children who become sick each year and require medicines as part of their care. Recent policy changes in the global medicines environment have also raised the profile of and the expectations for research with children. The Panel was committed to providing an assessment that could serve as a useful tool for improving knowledge about medicines for children. Their work points to ways in which research methods, collaborative approaches, and regulatory changes can help to improve the safety and efficacy of medicines. It is the hope of the Panel that this discussion will inform the continuing dialogue about developing medicines for children across many sectors in Canada and internationally.

ICH (International Conference on Harmonisation). (2000). *E11 Clinical Investigation of Medicinal Products in the Pediatric Population*. ICH.

IMS (IMS Health Canada Incorporated). (2013). *2012 Pediatric Drug Utilization*. Ottawa (ON): IMS Health Canada Inc.

OTHER COUNCIL REPORTS THAT MAY BE OF INTEREST:
Aboriginal Food Security in Northern Canada: An Assessment of the State of Knowledge

The State of Industrial R&D in Canada

The State of Science and Technology in Canada, 2012


EXPERT PANEL ON THERAPEUTIC PRODUCTS FOR INFANTS, CHILDREN, AND YOUTH: Stuart MacLeod (Chair), FCAHS, Professor of Pediatrics, Faculty of Medicine, University of British Columbia (Vancouver, BC); **Denise Avard,** Former Director of Research, Centre of Genomics and Policy; Associate Professor, Faculty of Medicine, Department of Human Genetics, McGill University (Montréal, QC); **Luis Barreto,** Special Advisor – Vaccine Program, Human Health Therapeutics Portfolio, National Research Council; President, Dr. Luis Barreto and Associates (Toronto, ON); **Brian Feldman,** Head of Rheumatology and Senior Scientist, Child Health Evaluative Sciences, Hospital for Sick Children; Professor, Pediatrics and Institute of Health Policy Management and Evaluation, University of Toronto (Toronto, ON); **Terry Klassen, FCAHS,** Director of Research, Manitoba Institute of Child Health (Winnipeg, MB); **David Knoppert,** Scientist, Division of Children’s Health and Therapeutics, Children’s Health Research Institute (London, ON); **Michael Kramer, FCAHS, FRSC,** Professor, Department of Epidemiology, Biostatistics, and Occupational Health and Department of Pediatrics, Faculty of Medicine, McGill University (Montréal, QC); **Catherine Litalien,** Pediatric Intensivist and Medical Director, Clinical Pharmacology Unit, CHU Sainte-Justine Research Centre (Montréal, QC); **Robert Nelson,** Senior Pediatric Ethicist/Deputy Director, Office of Pediatric Therapeutics, FDA (Silver Spring, MD); **Martin Offringa,** Staff Neonatologist and Senior Scientist, Child Health Evaluative Sciences, Hospital for Sick Children; Professor, Pediatrics and Institute for Health Policy Management and Evaluation, University of Toronto (Toronto, ON); **Robert Peterson,** Executive Director, Drug Safety and Effectiveness Network, Canadian Institutes of Health Research (Ottawa, ON); **Michael Rieder,** Professor, Department of Paediatrics, Physiology and Pharmacology and Medicine, Western University (London, ON); **Agnes Saint-Raymond,** Head of Human Medicines and Special Areas, European Medicines Agency (London, United Kingdom); **Wendy Ungar,** Health Economist and Senior Scientist, Child Health Evaluative Sciences, Hospital for Sick Children; Associate Professor, Institute for Health Policy Management and Evaluation, University of Toronto (Toronto, ON)



Council of Canadian Academies
Conseil des académies canadiennes

The Council of Canadian Academies is an independent, not-for-profit organization that began operation in 2005. The Council undertakes independent, authoritative, science-based, expert assessments that inform public policy development in Canada. Assessments are conducted by independent, multidisciplinary panels of experts from across Canada and abroad. Panel members serve free of charge and many are Fellows of the Council’s Member Academies. The Council’s vision is to be a trusted voice for science in the public interest. For more information about the Council or its assessments, please visit www.scienceadvice.ca.

This *Report in Focus* was prepared by the Council based on the report of the Expert Panel on Therapeutic Products for Infants, Children, and Youth.