Mind the Gap
Ensuring Effective and Safe Drug Therapy for Canada's Children

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Drug Therapy and Child Health

Historically childhood has been a dangerous time. Until the 1930's, the mortality rate for children across the world was 20% by age 6, i.e. one in every five children would die before their sixth birthday, usually of infection. Currently in Canada the under 6 mortality is 0.6%, with death being primarily due to congenital malformations or issues around labour and delivery such as extreme prematurity. This transformation – unparalleled in medical history – occurred due to three things and three things only – public sanitation, vaccination and effective drug therapy (Rieder 2010).

The impact of effective drug therapy on children's health cannot be over-estimated. While it is the impression that drugs are infrequently prescribed to children and that when they are they are only antibiotics, we have demonstrated that in fact Canadian children receive on average 4 prescriptions a year, more than 1,200 different drugs were prescribed from a wide range of therapeutic classes (Rieder *et al.* 2003). Research in the United States and Europe has demonstrated similar findings (Clavenna and Bonati 2009, Hales *et al.* 2018). Of key relevance, medication use is not uniformly distributed; 20% of children receive 70% of medications prescribed, typically children with complex and/or chronic disease.

This has had a huge impact on the wellbeing of these children. Diseases that were previously universally fatal now can be controlled and in many cases cured, childhood leukaemia being a prime example. Since the development of chemotherapy and after much arduous research to define best practice, childhood leukaemia is curable in up to 90% of cases. However, challenges remain as to disparity in outcome and, increasingly, access (Winestone and Aplenc 2019). These challenges will only become more profound as biologic, cellular and genetic treatments enter the therapeutic arena. As well, the substantial increase in prescribing for mental health issues in children and youth has added new complexity and questions, notably as it is now becoming increasingly clear that there are often substantial differences in the clinical manifestations of mental health disorders in children and youth than in adult and even more substantial differences in the efficacy and safety of psychoactive medications in children and youth than in adults. These challenges can only be addressed by well conducted research

Drug Research in Children and the Gap in Drug Therapy for Canadian Children

The Elixir of Sulfanilamide Tragedy and the Thalidomide Disaster, both of which were drug-induced events that primarily impacted children, changed drug regulation and the approach to research (Rieder 2010). While the changes in research and regulation that arose were intended

to make children's therapy safer, in fact they resulted in a significant lack of drug research for children, making children "therapeutic orphans" (Done *et al.* 1977). The impact of this gap on child health care was appreciated in the United States and Europe, with initiatives in both jurisdictions, including regulatory requirements for paediatric drug studies, resources in paediatric drug expertise at national regulatory agencies, dedicated national research support for drug research in children and dedicated national support for clinical trial networks for children. These initiatives – such as the US Better Pharmaceuticals for Children Act, the European Union's Paediatric Regulations and Connect 4 Children research network and the UK Medicines for Children have resulted in substantial enhancement in the availability of safe and effective drugs for children in the United States and Europe as well as generating evidence and knowledge that guides drug therapy for children world-wide (Roberts *et al.* 2003, Nordenmalm *et al.* 2018).

However despite these initiatives and similar work in places such as Australia, Canada has lagged behind both in regulation of drugs for children and in the provision of dedicated support for drug research in children (Hepburn *et al.* 2019, Moore-Hepburn and Rieder in-press). Canada is somewhat unique in not having dedicated Federal funding for drug research in children. While the existing grant panel structure at the Canadian Institutes of Health Research does include children in the mandate of some panels germane to drug therapy, these panels also evaluate drug studies in adults. Unfortunately the integration of children's and adult's drug research on grant panels tends to have the functional outcome of disappearance of the children's studies. This has created a gap in therapeutics for Canadian children, a gap that will only widen as the new biology identifies more molecular and genetic targets and as children's therapy becomes more complex (Canadian Council of Academies, 2014). The diversity of Canada's population of children – a source of national pride – also creates challenges in defining safe and effective drug therapy for children in the era of Precision Medicine (Elzagallaai *et al.* in-press). This gap is of particular relevance as high cost drugs increasingly become therapeutic options. A study we have just completed looking at drug policies in Children's Hospitals across Canada has identified high cost drugs as a major challenge to hospital budgets and a barrier to patient access (Pucchio and Rieder, in-press). This problem will only deepen as more drugs such as Onasemnogene abeparvovec (Zolgensma™), a gene therapy developed for a very serious children's disease, Spinal Muscular Atrophy, enter the market; at more than 2 million dollars, it is the most expensive drug ever marketed. There are never been a more pressing need for research to establish drug safety and efficacy in children, and to define drug utilization in a manner that best enhances the health of Canada's children.

This is particularly unfortunate as Canada is very positioned not only to bridge the gap but to be an international leader in drug research in children. Canada has the highest number of paediatric clinical pharmacologists per capita in the world, many of whom are internationally recognized as leaders in drug research in children (MacLeod *et al.* 2017). It is an unfortunate fact that much of this research is conducted in countries other than Canada, with Canadian experts serving on panels and collaborating on grant supported projects elsewhere. Laudable as this, it would be good if more of this expertise was being used in Canada.

Canada also is well positioned to conduct drug research in children given the demonstrated ability of child health researchers in Canada to work collaboratively through pan-Canadian networks. There are a number of highly successful networks, such as the Canadian Pharmacogenomics Network for Drug Safety, that have successfully conducted research by collaboration and cooperation that other, larger counties have not been able to emulate. The Maternal, Infant, Child and Youth Research Network is another excellent example of the power of bringing multiple networks together. One challenge that all Canadian networks face is the lack of long-term sustainable infrastructure support, an unfortunate issue that our American colleagues do not face.

Closing the Gap – Positioning Canada as a Leader in Researching in Safe and Effective Drug Therapy for Children

There is a pressing and immediate need to address the challenges that the dynamic and rapidly changing face of drug therapy for children presents to Canada's children, their families, their care-givers and the health care system. To address this, the following recommendations are proposed:

1. That Health Canada moves forward with Paediatric Regulations as part of Health Canada modernization, and that these regulations provide both incentives for drug research in children as well as mandates requiring drug research in children for drugs that are likely to be used by children. These considerations should include the issue of child-frineldy formulations for drugs to be used by younger children. These regulations should align with those in the United States and Europe to facilitate harmonized preparation of new drug submissions.
2. That Health Canada establishes a Paediatric Office with staff and a budget to support the office, including resources to develop and support a Paediatric Therapeutics Expert Advisory Group. This group would be composed of experts in paediatric pharmacology and drug therapy from across Canada as well as representatives from the community and key stakeholders in drug therapy for children. The Paediatric Office and Expert Advisory Group would in addition to evaluating new drug submission also monitor the paediatric therapeutic environment and serve to provide Health Canada and the Minister with timely expert advice on issues in paediatric drug therapy as they arise. The Expert Advisory Group should also be available as a resource for key partners in the children's therapeutic space.
3. That dedicated research funding at the Federal level be committed to support drug research in children. This funding should be brought forward on a multi-year basis and should be adjudicated and allocated by a grant panel with a specific mandate and expertise germane to drug research in children. The impact and outcomes of this research should be evaluated over time to assess the efficacy of this approach and to determine best resource allocation.
4. That dedicated and stable research funding be dedicated at the Federal level to support the infrastructure to support clinical research networks for children, particularly with respect to drug research in children. The impact and outcomes of these networks

should be reviewed on a regular basis but the “sunsetting” of network support that is common in Canada should be avoided if Canada is indeed hoping to position itself as an international leader in children’s research.

5. That training programs in clinical and drug research in children be enhanced and expanded, ideally through partnerships between academic institutions and the various levels of government, notably Federal and Provincial. These training programs should include learning best practices in patient and family engagement.
6. That public education programs on drug research in children and best drug therapy in children be developed in partnership with groups such as the Canadian Paediatric Society.

It is important to remember in perspective that children make up 25% of Canada’s population and 100% of Canada’s future.

Respectfully submitted

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