PUBLIC HEALTH AGENCY OF CANADA

CONGENITAL ANOMALIES IN CANADA 2013

A PERINATAL HEALTH SURVEILLANCE REPORT

PROTECTING CANADIANS FROM ILLNESS

Public Health Agency of Canada
Agence de la santé publique du Canada

Canada

TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP, INNOVATION AND ACTION IN PUBLIC HEALTH.
— Public Health Agency of Canada

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International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR)

European Surveillance of Congenital Anomalies (EUROCAT)

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FOREWORD

MESSAGE FROM THE DEPUTY CHIEF PUBLIC HEALTH OFFICER

I am pleased to present Congenital Anomalies in Canada 2013: A Perinatal Health Surveillance Report. This surveillance report provides comprehensive national data and information to improve our understanding of congenital anomalies in Canada.

Approximately 1 in 25 infants is diagnosed yearly with one or more congenital anomalies. For families, a congenital anomaly diagnosis can involve profound psychological, emotional and financial burdens. For those in public health, congenital anomalies are an important perinatal health issue due to the health resources they require for management and treatment and because of their ongoing impact on the health and well-being of Canadian infants, children and their families. On the bright side, public health strategies, such as folic acid food fortification and supplementation to prevent neural tube defects, have proven successful in Canada.

The Public Health Agency of Canada conducts national surveillance for congenital anomalies and other key indicators of maternal, fetal and infant health through the Canadian Perinatal Surveillance System. Maintaining quality health surveillance is a core role of the Agency and a crucial component in preventing and controlling congenital anomalies and other adverse perinatal outcomes. It serves to provide timely identification and communication of epidemiological trends, estimate the burden of congenital anomalies, shed light on potential teratogenic exposures and controllable risk factors, and guide research. It can also be used to inform reproductive and maternal and child health programs, services and policies so that they better meet the needs of Canadians who rely on them. To this end, the Agency continues to work in collaboration with the provinces and territories to improve congenital anomalies surveillance at all levels of public health.

It is my hope that this report will be a valuable resource for healthcare providers, government organizations and researchers to inform public health programs and support evidence-based decision making both in Canada and abroad. Our ultimate goal is to contribute to reducing the burden of congenital anomalies in Canada.

I would like to take this opportunity to thank the many volunteer experts who have dedicated much time and effort to the realization of this publication. The Public Health Agency of Canada is pleased to work with these individuals in our shared commitment to improving the health of Canadians.

Dr. Gregory Taylor
Deputy Chief Public Health Officer
Public Health Agency of Canada

INTRODUCTION

CONGENITAL ANOMALIES SURVEILLANCE IN CANADA, 2013

R. Brian Lowry
Juan Andrés León

This is the second national congenital anomalies surveillance report from the Public Health Agency of Canada's Canadian Perinatal Surveillance System (CPSS). The mission of the CPSS is to contribute to improved health for pregnant women, mothers and infants in Canada. Using data from 1998 to 2009, the report serves to support this mission and contribute to the Agency's important function to provide surveillance information.

The first report[1] followed an inaugural scientific meeting in Aylmer, Québec in 2000 to look at ways of improving Congenital Anomalies (CAs) Surveillance in Canada. Following that meeting, the Canadian Congenital Anomalies Surveillance Network (CCASN-hereafter referred to as the Network), was created in 2002 as part of the CPSS. The goals of the Network have been elaborated elsewhere.[2]

Congenital Anomalies in Canada, 2013 provides a concise overview of six important categories of CAs in Canada, including Down syndrome, neural tube defects, congenital heart defects, orofacial clefts, limb deficiency defects and gastroschisis. It presents national-level birth prevalence data and temporal trends; provincial and territorial estimates (including maps); and international comparisons.

Congenital anomalies, a term used synonymously with birth defects, are abnormalities that are present at birth, even if not diagnosed until months or years later. They are usually structural in nature and can be present from the time of conception (e.g., Down syndrome), but largely occur in the embryonic period (up to the end of the seventh week of gestation e.g., spina bifida), or in the early fetal period (eighth to sixteenth week). Occasionally they are the result of later events such as environmental insults in later gestation or exacerbation of pre-existing conditions after delivery (e.g., some forms of renal cysts).

In Canada, major CAs occur in approximately 3–5% of newborn infants and in 8% to 10% of stillbirths. They accounted for 23.2% of infant deaths from 2003–2007, including 23.3% of neonatal deaths, (i.e., deaths 0–27 days after birth).[3] CAs are second only to immaturity as a leading cause of infant deaths (1.1 and 1.5 per 1,000 live births, respectively) and contributed to an overall infant mortality rate of 5.0 per 1,000 live births for 2006–2007.[3]

The World Health Assembly at their 2010 meeting made a number of statements including the fact that they were "deeply concerned that Birth Defects are still not recognized as priorities in public health" and passed a resolution urging member states to:

> "raise awareness among all relevant stakeholders, including government officials, health professionals, civil society and the public about the importance of birth defects as the cause of child morbidity and mortality".[4]

The Second International Conference on Birth Defects and Disabilities in the Developing World in September 2005 resulted in the *Beijing Manifesto*, which called upon government leaders, health care providers and Non-Governmental Organizations in the developing world to take action, stating that:

> "until governments focus on preventing birth defects, infant mortality rates will continue to be unacceptably high and any decrease in childhood mortality will be hindered. We must continue to collaborate to establish and maintain birth defects surveillance and monitoring systems, foster research on the causes and prevention of birth defects and genetic diseases and establish sustainable technologically appropriate interventions for the prevention and care of these conditions including the provision of genetic services".[5]

Although significant steps have been made in Canada towards better national data, there is still much to be done. Correa and Kirby[6] have discussed areas of public health where CA surveillance data plays an important contributing role such as identifying health disparities and populations at risk, trend analysis, outcome evaluation, and including research and prevention. They also suggest that an increased focus on issues including environmental risk factors, classification of multiple and isolated CAs and enabling data linkages would further strengthen their application and utility.

In 2008 the Government of Canada announced *the Action Plan to Protect Human Health from Environmental Contaminants* which included a component to enhance CA surveillance nationally. The *Action Plan* made resources available to Canadian jurisdictions to either develop new surveillance systems or augment existing systems. Prior to this time only two of ten Provinces and none of the three Territories had surveillance systems dedicated to congenital anomalies. It is planned that national surveillance, which is currently conducted through the Agency's Canadian Congenital Anomalies Surveillance System (CCASS), will be enhanced as provincial and territorial systems become established or strengthened. The quality of data in regional, or provincial systems tends to be better than in national systems.[7,8]

This work, linking the Agency with Provinces and Territories, will maximize comparability across jurisdictions by promoting the use of common procedures for surveillance such as consistent data variables, definitions and collection methods. In other words, the proposed future model for CA surveillance in Canada is expected to function similar to that of the International Clearinghouse for Birth Defects Surveillance and Research,[9] EUROCAT[10] and the U.S. National Birth Defects Prevention Network (NBDPN)[11] and will result in an improved Canadian CA surveillance system.

WHAT CAN WE DO ABOUT PRIMARY PREVENTION?

Aside from single gene and chromosomally caused birth defects, the remaining CAs are largely multifactorial, i.e., caused by the interaction of genetic and environmental risk factors. Primary prevention strategies were given a huge boost by the success of folic acid supplementation, and more particularly, food fortification in the reduction of neural tube defects (NTDs) in Canada,[12] the United States[13] and Chile.[14] It takes a long time for a scientific discovery to become part of medical practice which, in the case of folic acid, took about 30 years and has been summarized by Rasmussen et al.[15] They also point out that the success of rubella vaccination in helping to eliminate Congenital Rubella Syndrome was due to public health surveillance and evaluation. In contrast, it is much harder to change human behaviour. This is exemplified by the association between alcohol use and Fetal Alcohol Spectrum Disorder, which is entirely preventable.

Quality information on risk factors is essential for developing strategies for primary prevention. Good data are also emerging with respect to socioeconomic status, maternal obesity, control of diabetes, smoking, and the potential benefits of multivitamin and folic acid usage. Although there is an increasing body of literature on the effects of environmental factors such as land waste sites, air quality, pesticides, electromagnetic fields, as well as occupational exposures, the evidence is conflicting and hence does not allow primary prevention strategies. Therefore, research that overcomes the limitations of the evidence on these environmental factors and occupational exposures needs to be undertaken. Public health initiatives to reduce or prevent exposures to well known risk factors such as alcohol use, lack of rubella and varicella immunization, as well as known teratogenic drugs such as anti-epileptics (e.g., Valproic Acid, Carbamazepine), Thalidomide, Isotretinoin, and ACE Inhibitors should be strengthened. Pharmacogenetic research may, in the future, aid in the identification of women at higher risk for drug induced birth defects.

Obesity is becoming an increasing problem in Canada, the United States and indeed in the developing world. While pre-pregnancy obesity (body mass index (BMI) ≥ 30 kg/m^2) has been suspected as a risk factor for many years, only in the past decade has the evidence become more compelling[16-19] especially for NTDs[17] and for selected forms of congenital heart disease.[19] Other CA categories that have been observed to be associated with maternal obesity are cleft palate, cleft lip with or without cleft palate, anorectal atresia, hydrocephalus and limb deficiencies.[18] There is an inverse relationship between obesity and gastroschisis as the latter outcome is more often related to low prepregnancy BMI in addition to young maternal age.

Carmichael et al. discussed the underlying mechanisms that may be responsible for the increased CA risk for obese and even overweight women (BMI 25–29.9 kg/m^2). [20] They include nutrition and glycemic control related mechanisms. Maternal obesity also increases the risk for perinatal and postnatal problems. Weight reduction prior to pregnancy thus can be a primary preventive method. It is an accepted fact that the increased risk of CAs in poorly controlled diabetic mothers can be reduced to that of the general population risk with good glycemic control.

Differences in the occurrence of disease and other health outcomes by socioeconomic status (SES) are indicators of disparities in health. SES is usually estimated by parental income, education, occupation or area of residence. Ethnicity is also an influential factor but cannot easily be obtained from Canadian databases as this information is lacking on most birth registrations and similar documents. Infant mortality and morbidity are higher in those whose parents have lower incomes, even in countries such as Canada and the United Kingdom where there is universal healthcare, indicating the importance of a broad range of determinants of health.[21]

Individuals within families of lower SES index often have other risk factors such as cigarette smoking, alcohol drinking, poor nutrition, obesity and lack of multivitamin supplements. Carmichael et al.[22] adjusted their results for most of these factors and still found an association between low SES and increased risk of D-transposition of the great arteries (dTGA), as well as a decreased risk of tetralogy of Fallot (TOF). There was no association with risk of orofacial clefts. No other types of anomalies were studied. Yang et al.,[23] using data from an NBDPN study, found low maternal education was associated with elevated risk for anencephaly and dTGA, while low paternal education increased anencephaly, cleft palate, TOF, and dTGA risks.

It seems all too evident that reduction of socioeconomic inequalities will contribute to reduce the birth prevalence of some CAs, but this will require broadly based societal changes such as providing opportunities and access to full employment, assisted housing and more education. This is a national public health challenge requiring collaboration across many sectors and ongoing public health surveillance and evaluation.

SUMMARY

The new thrust in reducing the burden of CAs is primary prevention, but first we must have good quality surveillance data to provide reliable provincial, territorial and national prevalence rates. Prevalence rates and primary prevention are the subjects of several chapters in this report. Secondary prevention and management of selected congenital anomalies are dealt with in separate chapters.

Folic acid has proven its effectiveness for prevention of NTDs and when combined with multivitamins, may reduce the risk for certain other congenital anomalies. Behavioural changes in the population will be required as part of the preventive efforts to reduce or even eliminate the health consequences associated with smoking, alcohol intake, overweight and obesity. These will be much harder to achieve and require effective interventions in the preconception period. The initiative to enhance CA surveillance nationally, developed by the Agency in collaboration with volunteer experts from the Network, is a significant step forward in the prevention of CAs in Canada.

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CHAPTER 1

OVERALL PREVALENCE AND KEY DEMOGRAPHIC FACTORS

Jane A. Evans
Chantal Nelson

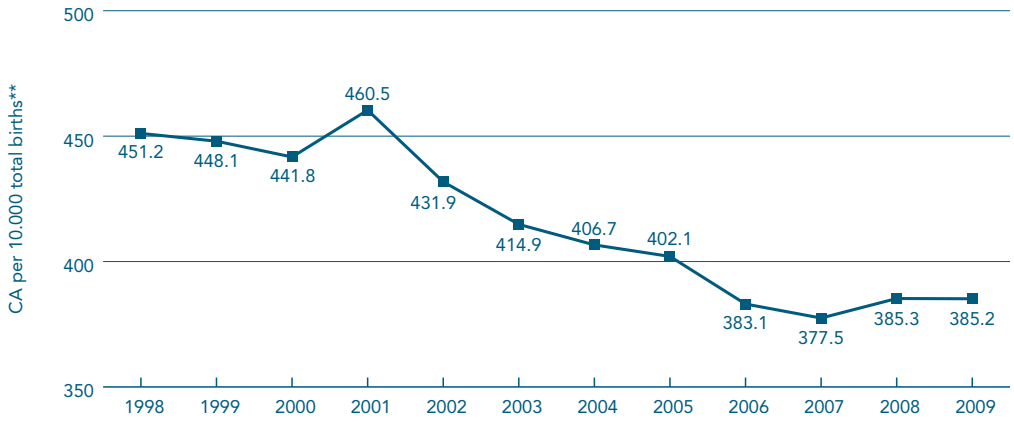
In order to evaluate the impact of congenital anomalies on individuals, families and the public health system, it is important to have reliable estimates of the number of affected births. This is not straightforward as factors such as sources for case ascertainment, criteria for inclusion and exclusion and length of time of follow-up will all impact on the overall birth prevalence. Currently, the Public Health Agency of Canada's Canadian Congenital Anomalies Surveillance System (CCASS) uses discharge abstract data (DAD) on newborns, collected from provincial and territorial hospitals via the Canadian Institute for Health Information (CIHI) and the Québec Système de maintenance et d'exploitation des données pour l'étude de la clientèle hospitalière (MED-ÉCHO). More detailed provincial data are also submitted to CCASS by the Alberta Congenital Anomalies Surveillance System (ACASS). The CCASS data from CIHI are limited for surveillance purposes in several ways: they rely on invalidated International Classification of Diseases (ICD) codes; the anomalies are only ascertained in infants less than 30 days of age because of administrative reasons (Appendix A); they do not contain easily available information on gestational age; and they are restricted to live births and stillbirths, thus not allowing capture of terminations of pregnancy for congenital anomalies before 20 weeks of gestation.[1] Using MED-ÉCHO data is also problematic as there are differences in the coding of anomalies in stillbirths and in inclusion and exclusion criteria, especially with respect to less well defined and/or minor defects.

In this report, most data on the six types of anomalies selected for review are largely based on CCASS data for all provinces and territories from 1998–2007. This section on overall prevalence rates and key demographic factors is based on a slightly different data set in order to be both more current and more consistent. It includes cases from 1998–2009 but relies only on CIHI data, thus Québec cases are excluded.

The total frequency of major congenital anomalies in live births and stillbirths is often estimated to be 3–5%, though few surveillance systems report an overall figure because of considerable variation in ascertainment, definitions and inclusion/exclusion criteria. CCASS data for seven provinces—British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Prince Edward Island and Newfoundland and Labrador (approximately 70% of births)—indicated a rate of 420.1 per 10,000 total births (live births and stillbirths) in 1984–1986 and a similar rate of 423.1 per 10,000 in 1991–1993.[2] Figure 1.1 shows the prevalence trend in total births from 1998 to 2009 and indicates that rates have declining over this time period. The higher rates during 1998 to 2001 compared to those noted after 2001 may be due to better ascertainment. Part of the decline subsequent to 2001 can be attributed to a shorter ascertainment period from one year to 30 days. Other factors may include increasing use of prenatal diagnosis and screening and a reduction in certain malformations, especially neural tube defects, since the mandatory fortification of certain grain products with folic acid in 1998.

FIGURE 1.1

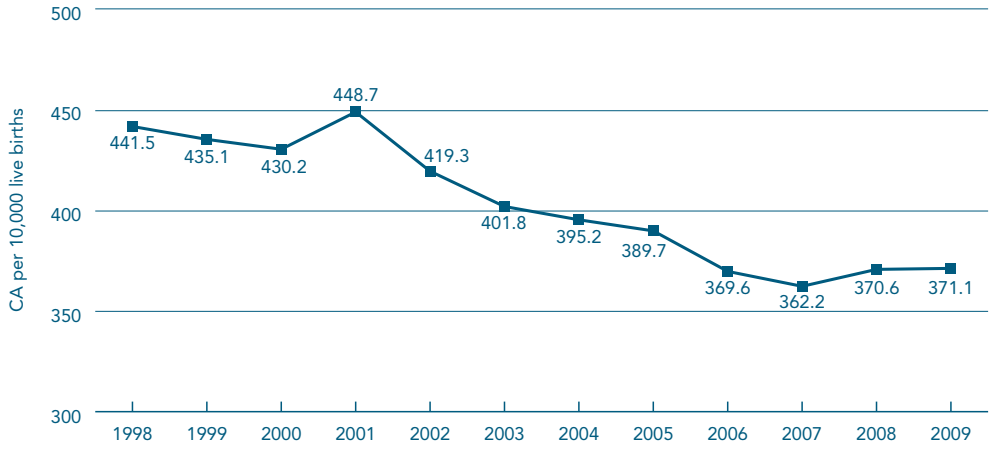
Total congenital anomaly (CA) rate, *Canada (excluding Québec),* 1998–2009*



Source: Public Health Agency of Canada. Congenital Anomalies Surveillance System, 1998–2009.
*Québec was excluded because data were not available for all years.
**Total births include live births and stillbirths.

FIGURE 1.2

Total congenital anomaly (CA) rate in live births, *Canada (excluding Québec),* 1998–2009*

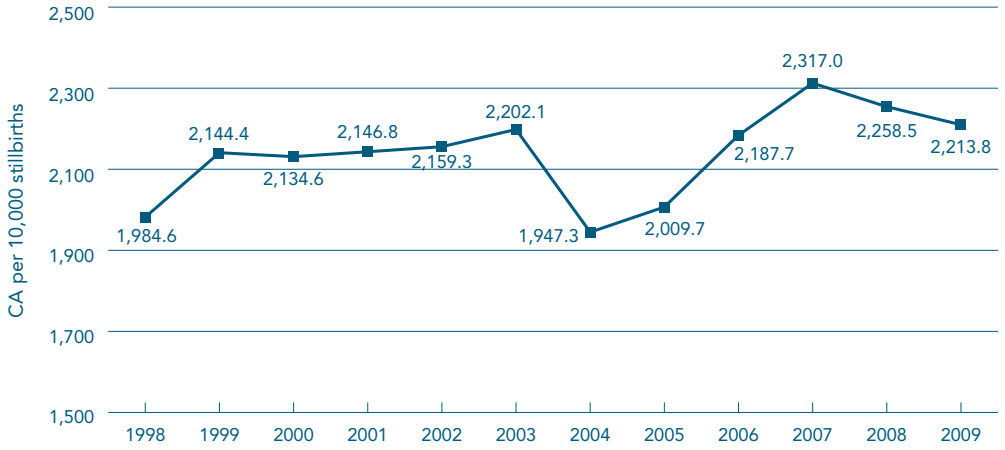


Source: Public Health Agency of Canada. Congenital Anomalies Surveillance System, 1998–2009.
*Québec was excluded because data were not available for all years.

Figure 1.2 indicates that the decrease in rates among live births has been notable, leading to a birth prevalence below 400 per 10,000 in 2009. However, as can be seen from Figure 1.3, the rates in stillbirths seem to have increased slightly. This is largely due to an increase in congenital anomalies in stillbirths of low birth weight, such that over three-quarters of the congenital anomalies in stillbirths are seen in fetuses less than 750 g (Figure 1.4). There has also been a significant increase in the proportion of malformed stillbirths for which no birth weight is available. These factors suggest that most of the increase of congenital anomalies in stillbirths (and the concomitant decrease in live births), is due to a higher frequency of terminations of pregnancy for fetal malformation at 21–24 weeks continuing a trend that has been previously documented.[3] The true impact of prenatal diagnosis and pregnancy terminations on stillbirths is, however, difficult to assess as the coding of the cause of a stillbirth as due to congenital malformation or termination of pregnancy can be somewhat arbitrary and is not consistent across jurisdictions.

FIGURE 1.3

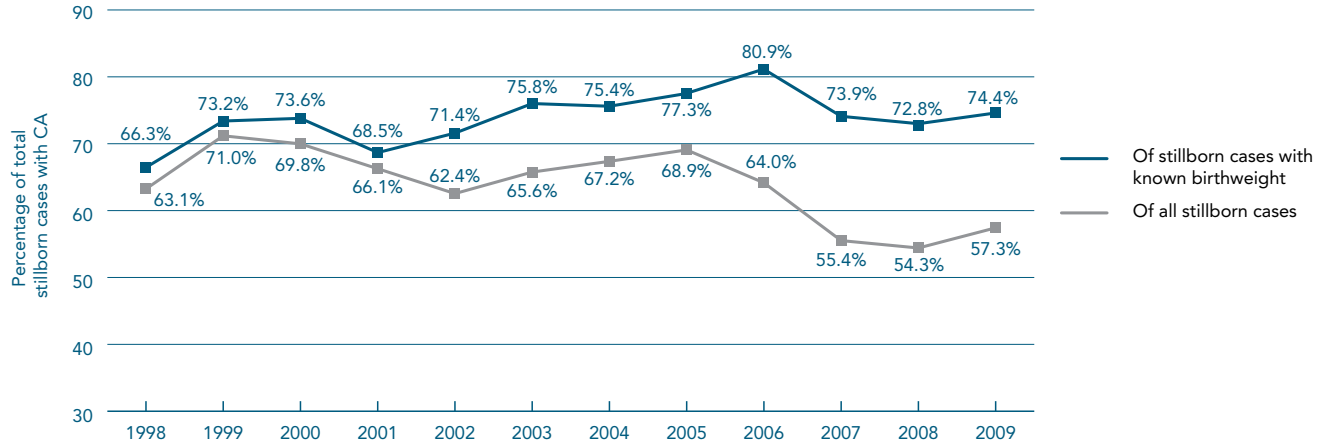
Total congenital anomaly (CA) rate in stillbirths, *Canada (excluding Québec),* 1998–2009*



Source: Public Health Agency of Canada. Congenital Anomalies Surveillance System, 1998–2009.
*Québec was excluded because data were not available for all years.

FIGURE 1.4

Percentage of stillborn congenital anomaly (CA) cases <750 g, *Canada (excluding Québec),* 1998–2009*

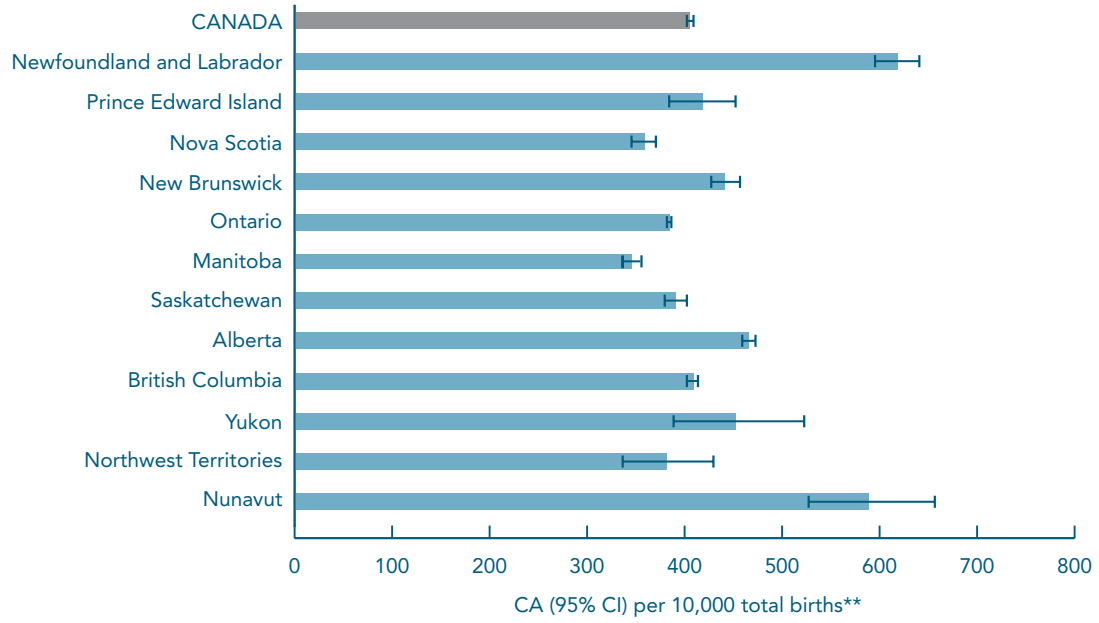


Source: Public Health Agency of Canada. Congenital Anomalies Surveillance System, 1998–2009.
*Québec was excluded because data were not available for all years.

From Figure 1.5A, it can be seen that there are variations in rates between provinces and territories ranging from a low of 347.8 (95% CI: 338.2–357.6) per 10,000 total births in Manitoba to a high of 622.1(95% CI: 599.6–645.3) per 10,000 total births in Newfoundland and Labrador. Confidence intervals are wide in those areas where the numbers of cases are small (fewer than 40 per year in each of the Territories). Thus rates from such jurisdictions should be interpreted with caution. In addition, many factors will influence regional variation, including methods of case ascertainment and coding, the availability of prenatal diagnosis and screening services and their utilization, as well as the likelihood of pregnancy termination of prenatally diagnosed cases.

FIGURE 1.5A

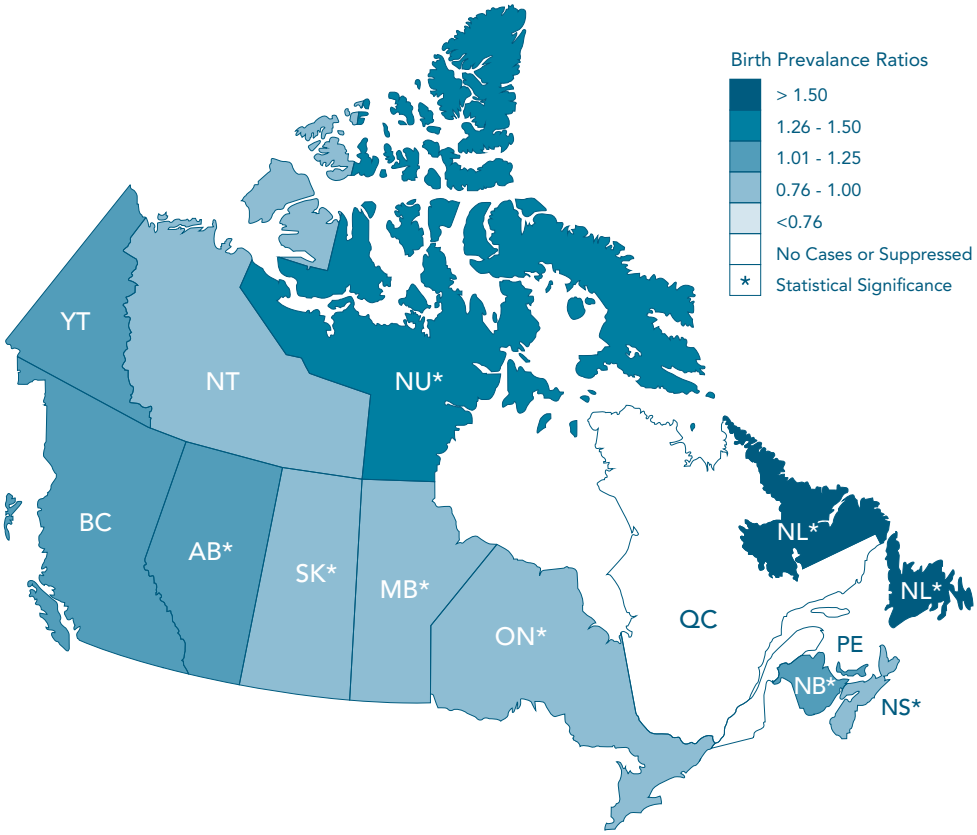
Total congenital anomaly (CA) rate, by province/territory, *Canada (excluding Québec),* 2000–2009 combined*



Source: Public Health Agency of Canada. Congenital Anomalies Surveillance System, 2000–2009.
*Québec was excluded because data were not available for all years. **Total births include live births and stillbirths. CI—Confidence Interval

FIGURE 1.5B

Ratio of provincial/territorial congenital anomaly rate to national rate,** *Canada, (excluding Québec) 2000–2009 combined*

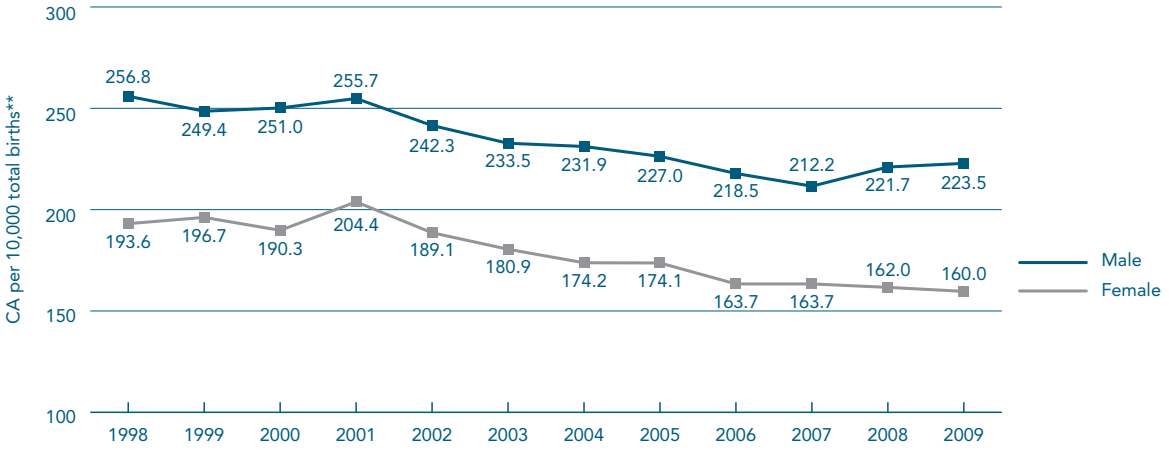


Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 2000–2009.
**This ratio calculates the birth prevalence rate per 10,000 total births of each individual province/territory to the birth prevalence rate for Canada during the specified time period. The birth prevalence for Canada includes cases for which province/territory is unknown.
***Québec was excluded because data were not available for all years.

It has long been recognized that overall congenital anomaly rates, and those for the majority of individual defects, are higher in males.[4] From Figure 1.6, it can be seen that the birth prevalence has fallen for both sexes. However, the ratio of male to female cases has increased slightly with time (Figure 1.7). This could be due to a variety of factors including higher rates of specific anomalies that are restricted to males (hypospadias), or are more common in males, such as Down syndrome and renal agenesis. It could also be due to sex differences in rates of survival, early termination for fetal anomaly or the differing impact of preventive strategies such as folic acid fortification on male and female fetuses. Another factor could be a relative increase in multiple congenital anomalies, which are more common in males.

FIGURE 1.6

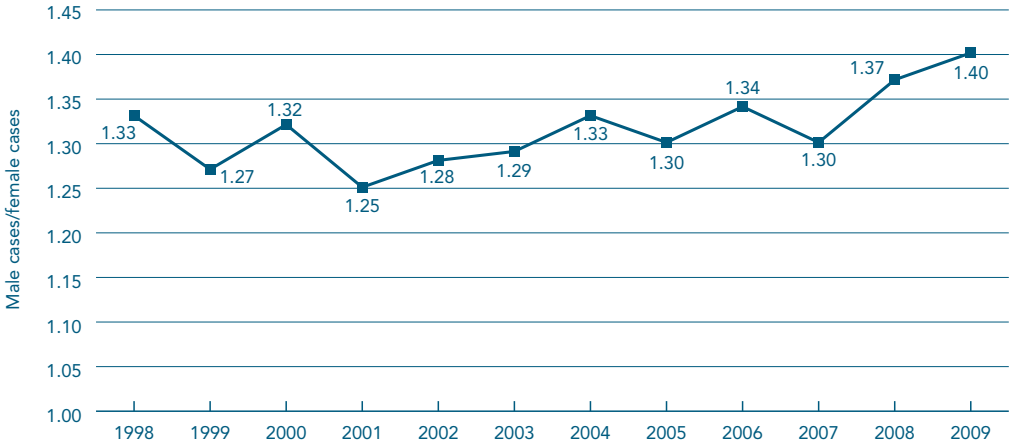
Total congenital anomaly (CA) rate, by gender, *Canada (excluding Québec),* 1998–2009*



Source: Public Health Agency of Canada. Congenital Anomalies Surveillance System, 1998–2009.
*Québec was excluded because data were not available for all years. **Total births include live births and stillbirths.

FIGURE 1.7

Ratio of total male to total female congenital anomaly cases, *Canada (excluding Québec),* 1998–2009*



Source: Public Health Agency of Canada. Congenital Anomalies Surveillance System, 1998–2009.
*Québec was excluded because data were not available for all years.

The inability to easily differentiate isolated birth defects from various patterns of multiple congenital anomalies (syndromes, sequences, associations, etc.) in the CCASS data is another drawback of the current system. An exploratory analysis of orofacial clefts (OFCs) divided cases into those with a single code for a CA and those with codes in addition to the one for the OFC. While it has not yet been possible to validate whether this adequately distinguishes isolated cases from those with other anomalies, the data do indicate that the decline in cleft lip with or without cleft palate (CL ± CP) observed over time (see Chapter 5), appears to be more pronounced for "isolated" cases than for more complex ones. In addition, the ratio of "isolated" to complex ones appears to differ between provinces.

Further use of Canadian surveillance data to evaluate trends in multiple anomalies, as has been explored by others,[5,6] would clearly be worthwhile. Many risk factors, including environmental teratogens, can cause multiple CAs (e.g., limb deficiencies, heart defects and intestinal atresias with thalidomide, central nervous system defects and OFCs with maternal hyperthermia) or combinations of major and minor defects (e.g., in Fetal Alcohol Syndrome). Thus more detailed analysis of anomaly codes would add considerably to the value of surveillance data for monitoring the impact of environmental risk factors. For example, a case definition including codes for ear defects, certain central nervous system defects and selected heart malformations was used by the Atlanta Birth Defects Surveillance System to identify cases of isotretinoin embryopathy with a sensitivity of 45.5% and a specificity of 99.9%. The positive predictive value of the combination was 85%.[6]

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CHAPTER 2

DOWN SYNDROME

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Jocelyn Rouleau

INTRODUCTION

Down syndrome (DS) is one of the most common congenital anomalies worldwide, occurring in approximately 1 in 800 births.[1,2] This chromosomal disorder, associated with the presence of extra chromosome 21 material, is characterized by a well-defined phenotype, intellectual delay, and a number of major and minor congenital anomalies; most commonly, congenital heart and gastrointestinal defects.[1,2]

Babies with chromosomal disorders, including DS, tend to be small in size and have low birth weight. Very low birth weight (401 to 1500 g) has been reported to be twice as prevalent among infants with DS as among total births.[3] Excluding complications of low birth weight, the overall one-year survival of DS infants with and without congenital heart defects has been reported between 78–90% and 93–97% respectively.[4]

Congenital heart defects and respiratory infections are the most frequently reported causes of deaths in children and young adults with DS.[4] Childhood leukemia is commonly associated with DS, whereas other malignancies are less frequent than expected.[5] Awareness and monitoring of potential medical health risks and early intervention greatly decrease morbidity and improve the quality of life among individuals with DS.[6]

RISK FACTORS

Advanced maternal age is the most significant established risk factor for DS. Prenatal screening has advanced in both accuracy and early detection such that it has had a significant impact on the DS live birth prevalence across all maternal ages, worldwide. This will be further discussed in Chapter 9.

In addition to advanced maternal age, having a previously affected child or other family history of DS are additional risk factors that warrant referral for genetic counselling. The recurrence risk for fetal trisomy after having had one affected child is roughly 1%. A family history of DS and/or recurrent miscarriages may suggest that a chromosome translocation involving chromosome 21 is segregating within the family, which can be confirmed or ruled out by parental karyotyping.

PREVALENCE RATE OF DOWN SYNDROME IN CANADA

As depicted in Figure 2.1, the birth prevalence of Down syndrome in Canada for 1998–2007 was relatively constant, averaging 14.1 per 10,000 total births. This rate was similar to previously reported rates for 1989–1997.[7] Both the live birth and stillbirth DS rates have also remained relatively stable at 12.4 and 1.7 per 10,000 total births, respectively. Congenital heart defects were reported in 40.9% of DS cases, of which 98% were reported as live births.

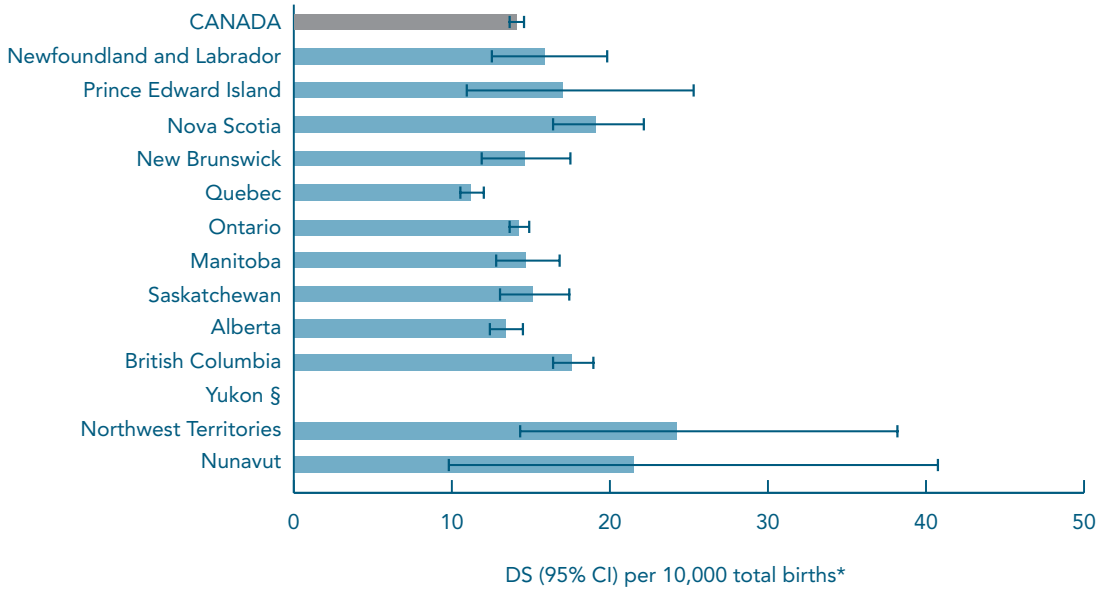
FIGURE 2.1

Down syndrome (DS) rate, *Canada, 1998–2007*

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1998–2007.
*Total births include live births and stillbirths.

FIGURE 2.2A

Down syndrome (DS) rate, by province/territory, *Canada, 1998–2007 combined*



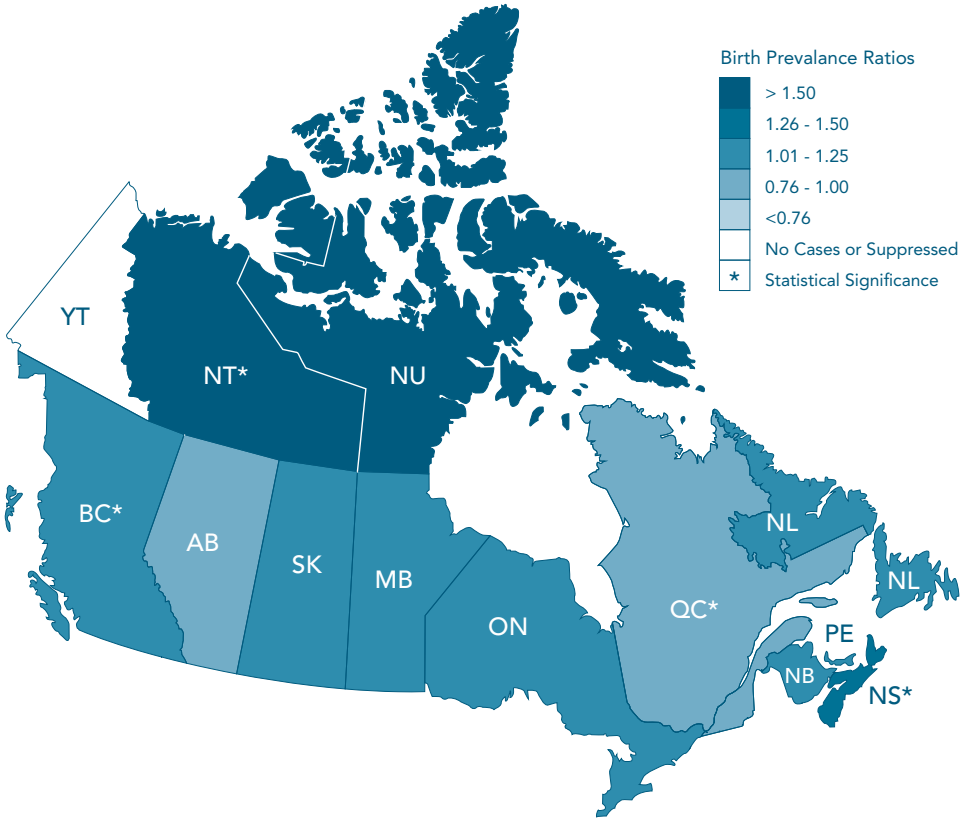
Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1998–2007.
*Total births include live births and stillbirths.
§Rate suppressed due to small cell counts (<5). CI—Confidence Interval

PROVINCIAL AND TERRITORIAL PREVALENCE RATES

Variation exists in the provincial and territorial DS birth prevalence rates (live births and stillbirths) for the ten years combined (Figure 2.2A and 2.2B). The DS rate ranged from 11.2 (95% CI: 10.5–12.0) in Québec to 21.5 (95% CI: 9.8–40.8) and 24.2 (95% CI: 14.3–38.3) in Nunavut and Northwest Territories respectively. Given the low number of cases and total births (see Table B2.2 in Appendix), the high rates in the less populated northern territories may be due, in part, to chance and should therefore be interpreted with caution.

FIGURE 2.2B

Ratio of provincial/territorial Down syndrome rate to national rate,** *Canada, 1998–2007 combined*



Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1998–2007.
**This ratio calculates the birth prevalence rate per 10,000 total births of each individual province/territory to the birth prevalence rate for Canada during the specified time period. The birth prevalence for Canada includes cases for which province/territories is unknown.

Advanced maternal age, as well as access to, and utilization of prenatal diagnosis and selective termination of affected pregnancies influence the birth prevalence of DS. Eighteen percent of total births in Canada were to mothers 35 years of age or older in 2007.[8] Although the reported DS birth prevalence rate in Nunavut was high, the proportion of births to women over 35 years of age in this territory was the lowest in Canada (8%) in 2007. A similar observation was noted in the Northwest Territories.

Roughly 60% of all births occur in the provinces of Québec (21.7%) and Ontario (39.4%). A comparison of DS live birth rates from 1998 to 2007 for these two provinces is presented in Table 2.1. The DS live birth rate in Québec was significantly lower than in Ontario for the combined years (10.8 versus 12.5, respectively). Further, 15.4% of live born deliveries were to women of over 35 years in Québec compared with 21.2% in Ontario in 2007 (rates similar for 2003 to 2006).[8] There was a significant difference in live birth rates of DS between the two provinces in 2006 and 2007. A downward trend is noted in Québec that is not seen in Ontario. As the data sources for live birth in these two provinces are very comparable, this suggests that access to prenatal diagnosis and resulting termination of DS pregnancies may be higher in Québec compared to Ontario.

TABLE 2.1

Down syndrome (DS) rate in live births, *Ontario and Québec, Canada, 1998–2007*

Year	Ontario DS rates per 10,000 live births (95% CI)	Québec DS rates per 10,000 live births (95% CI)
1998	10.6 (8.9–12.4)	13.4 (10.9–16.3)
1999	13.3 (11.4–15.4)	12.3 (9.9–15.2)
2000	13.0 (11.1–15.1)	11.9 (9.5–14.7)
2001	12.9 (11.0–14.9)	9.4 (7.3–12.0)
2002	12.8 (11.0–14.9)	10.2 (8.0–12.8)
2003	13.6 (11.7–15.8)	10.5 (8.3–13.2)
2004	11.9 (10.1–13.8)	11.5 (9.1–14.2)
2005	10.9 (9.3–12.8)	12.1 (9.8–14.9)
2006	14.0 (12.1–16.1)	9.1 (7.2–11.4)
2007	12.1 (10.3–14.0)	7.9 (6.1–10.0)
1998–2007	12.5 (11.9–13.1)	10.8 (10.1–11.6)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2007.
CI—Confidence Interval

TABLE 2.2

Down syndrome (DS) rate, by maternal age, *Alberta, Canada, 2000–2004, 2005–2009 and 2000–2009*

Year	DS rate by maternal age (95% CI)*						
	<20	20–24	25–29	30–34	35–39	≥40	Total
2000–2004	8.0 (3.7–15.1)	6.4 (4.2–9.5)	10.7 (8.2–13.7)	16.6 (13.4–20.4)	52.4 (43.7–62.4)	143.1 (110.3–182.8)	19.6 (17.7–21.7)
2005–2009	7.6 (3.5–14.4)	7.3 (5.0–10.3)	10.7 (8.5–13.3)	16.8 (13.9–20.1)	53.8 (45.9–62.6)	189.3 (156.1–227.8)	21.8 (19.9–23.7)
2000–2009	7.8 (4.6–12.3)	6.9 (5.2–8.9)	10.7 (9.0–12.6)	16.7 (14.5–19.1)	53.2 (47.3–59.7)	169.5 (145.5–196.5)	20.8 (19.5–22.2)

Source: Alberta Congenital Anomalies Surveillance System, 2011.
*Per 10,000 total births. Total births include live births, stillbirths and terminations of pregnancy.
CI—Confidence Interval

TABLE 2.3

Down syndrome international rates,* by region/country, *1998–2007*

Region/country	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
CANADA†	14.2	14.5	15.1	13.3	14.1	15.0	13.4	14.9	13.8	13.0
Alberta, Canada	14.0	11.6	14.6	15.2	12.7	19.2	16.5	20.5	13.4	16.4
Atlanta, USA	11.5	12.0	11.1	13.2	12.5	13.0	13.0	12.9	10.9	13.1
Paris, France	10.5	5.2	7.9	7.8	6.2	4.7	5.3	9.1	7.1	8.7
Tuscany, Italy	6.3	6.1	4.9	5.7	3.8	4.0	4.1	4.1	4.6	4.8
Finland	11.3	10.0	11.8	14.2	14.2	12.3	12.2	11.7	14.2	14.0

Source: International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) Annual Report, 2009 (data from 2007)
†Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 2007.
*Rate per 10,000 total births. Total births include live births and stillbirths.

Regional differences in maternal age-specific total prevalence rates of DS are not available. Data from the province of Alberta that include terminations of pregnancy are outlined in Table 2.2. Mothers over 35 years of age had significantly higher DS prevalence rates than mothers aged 25–29 years during the combined years 2000–2009.

INTERNATIONAL COMPARISONS

In 2007, there were 1,430,697 DS births among 23 worldwide surveillance programs reporting to the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR).[9] Canada reported 483 cases through the Canadian Congenital Anomalies Surveillance System (CCASS) for that period. DS birth prevalence rates from 1998 to 2007 among a sample of ICBDSR registries are presented in Table 2.3.

In a study including 20 ICBDSR registries between 1993 and 2004, the overall prevalence of DS remained relatively stable at 8.3 per 10,000 total births (live and stillbirths).[10] During this time period, however, the birth prevalence of DS decreased in registries in France and Italy, and increased in others including Israel, Norway and Alberta, Canada. The mean termination rate of DS confirmed pregnancies among the 20 registries increased from 4.8 per 10,000 total births in 1993 to 9.9 in 2004.

TABLE 2.4

Percentage of mothers ≥35 years and Down syndrome terminations;
Down syndrome rate in live births, stillbirths and terminations, by region/country, *2007*

Region/Country	% of mothers ≥35 yr	% of terminations in mother ≥35 yr	Prevalence rate (per 10,000)	
			LB+SB	LB+SB+ terminations
Texas, USA	11.4	5.4	49.3	52.1
Alberta, Canada	15.5	40.0	51.5	85.9
Atlanta, USA	17.0	17.0	39.0	48.3
Sweden	21.7	73.2	18.2	67.6
Paris, France	28.6	83.1	8.0	47.5
Tuscany, Italy	32.1	70.6	10.1	34.2

Source: International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) Annual Report, 2009 (data from 2007).
LB—Live Birth, SB—Stillbirth

IMPACT OF PRENATAL DIAGNOSIS ON BIRTH PREVALENCE OF DOWN SYNDROME

The impact of maternal age and prenatal diagnosis on the DS prevalence rate, according to the ICBDSR Collaborative Research Project,[9] is presented in Table 2.4. Improved access and performance of prenatal screening are believed to have offset the effect of increased rates in advanced maternal age at birth throughout various jurisdictions. According to this international study, the greatest termination rates are in registries that show higher percentages of advanced maternal age mothers.

The impact of prenatal diagnosis on the DS birth prevalence rate in Canada requires provincial and territorial termination data. With the exception of Alberta, termination data are not currently reported by provincial and territorial congenital anomalies surveillance systems, nor are they captured by CCASS.

For the combined years 1998–2007, age-specific data from the Alberta Congenital Anomalies Surveillance System did not demonstrate the maternal age specific variation in termination rates seen in 2007 by ICBDSR (Table 2.4). For the 10 years combined in Alberta, 52.4% of the total confirmed DS pregnancies occurred among women 35 years of age or older; of these, 24% (range: 16.9% to 30.5%) were terminated, which was a similar rate to that seen for women less than 35 years of age.

The Society of Obstetricians and Gynaecologists of Canada (SOGC) published clinical care guidelines for prenatal testing[11] that advise against using maternal age as the sole indication for invasive prenatal diagnosis. They recommend that prenatal screening for clinically significant fetal aneuploidies be offered to all pregnant women. However, the methods used for screening and their availability vary between and even within provinces. Moreover, the uptake of screening and utilization of prenatal diagnosis is not captured within a single national registry.

SUMMARY

Down syndrome remains the most frequently occurring chromosome anomaly in Canada and has an impact on infant morbidity and mortality as well as childhood and adult morbidity. Despite the rising rates of advanced maternal age at delivery, the national birth prevalence rates have remained stable over the 1998–2007 time period. This is most likely due to increased access and utilization of prenatal screening and testing and subsequent termination of pregnancies affected with aneuploidy.

Continuing population-based surveillance and research relating to the impact of prenatal testing on the birth prevalence rates and the impact of various pre- and postnatal factors that influence the morbidity and mortality of babies born with DS is of great public health importance in Canada.

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CHAPTER 3

NEURAL TUBE DEFECTS

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INTRODUCTION

Neural tube defects (NTDs) are a group of heterogeneous anomalies of the central nervous system caused by defective closure of the neural tube during embryogenesis. The most common NTDs are spina bifida, anencephaly, and encephalocele. Anencephaly is lethal. Spina bifida patients experience substantial morbidity throughout life, and elevated mortality rates.[1]

RISK FACTORS

NTDs can occur in chromosomal disorders, genetic syndromes and other patterns of multiple malformations or be the result of an environmental teratogen. In such cases, other congenital malformations are often present. Most NTDs, however, are isolated defects due to multifactorial inheritance (i.e., the interaction of genetic and environmental risk factors). In such cases, the recurrence risk is 2–5% depending on baseline population risk, but can be significantly reduced by periconceptional folic acid supplementation.[2]

Folate deficiency[3] is the most well established risk factor for isolated NTDs. Inadequate intake of folic acid from all sources (foods naturally rich in folate, foods fortified with folic acid and folic acid containing supplements) remains an important modifiable risk factor in Canada and throughout the world.

Fetuses of mothers who have the C677T variant of the gene coding for 5,10-methylenetetrahydrofolate reductase, an enzyme involved in folate metabolism, are at increased risk for spina bifida[4] and anencephaly.[5] Potentially other enzyme variants also increase risk. Other risk factors whose association to folate metabolism is less clear include certain ethnic backgrounds (e.g., Celtic populations, Sikhs, French Canadians, Hispanics),[6] maternal obesity,[7] pre-gestational diabetes[8] and other forms of hyperglycemia.[9]

Non-folate sensitive NTDs include some isolated forms such as lipomyelomeningoceles,[10] those due to certain environmental exposures (e.g., valproic acid,[11] hyperthermia[12]), or suboptimal intake of other micronutrients (e.g., vitamin B12[13]), as well as those seen in patterns of multiple malformations. Risks for these disorders would not be impacted by food fortification with folic acid or supplementation and thus they may be becoming proportionately more common as causes of NTDs.

PREVALENCE RATE OF NEURAL TUBE DEFECTS IN CANADA

The prevalence rate of all NTDs (including spina bifida) in Canada declined between 1996 and 2007 (Figure 3.1). After falling sharply between 1997 and 1998, following the introduction of folic acid-fortified flour on the North American market,[14-16] the prevalence of NTDs in general and spina bifida in particular, continued to decline between 1999 and 2004, before leveling off. These trends are similar to those observed by De Wals et al.,[14] who noted a decline in seven Canadian provinces post-fortification. However, anomaly rates reported by the Canadian Congenital Anomalies Surveillance System (CCASS) are much lower than those from De Wals' study. This is due in large part to the exclusion of terminations before 20 weeks by CCASS.

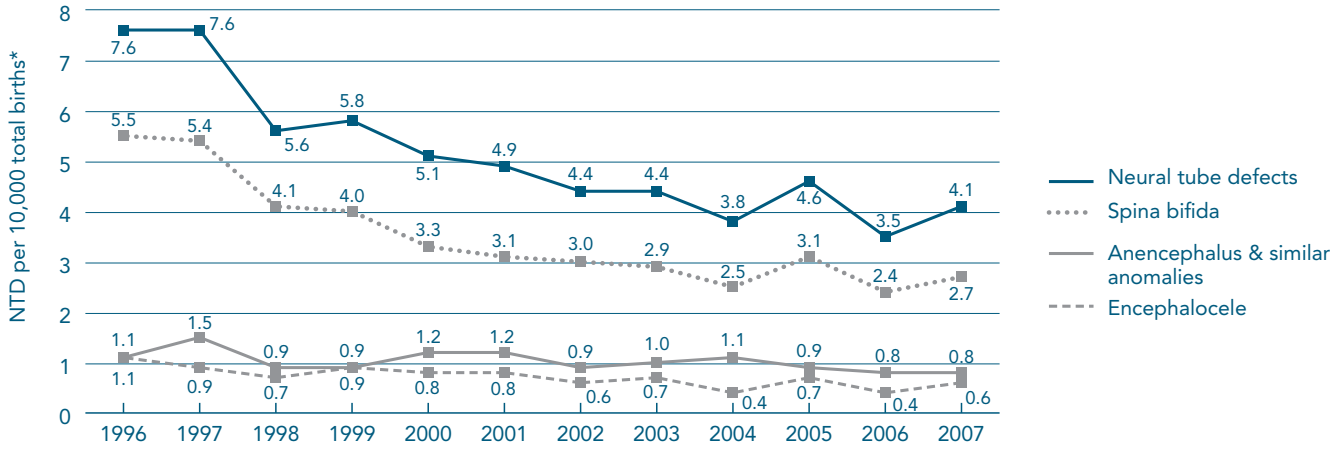
Based on the time course of population levels of blood folate, it is assumed that births that occurred before or during 1996 were conceived and had their first gestational trimester in the pre-fortification

period. Those that occurred in 1998 and 1999 were conceived and had their first trimester while some fortified food was available on the Canadian market but before fortification became mandatory, and those that occurred in 2001 were conceived in the full fortification period.[15] Compared to births from the end of the pre-fortification era (i.e., 1996), those from the early post-fortification era (i.e., 2001–2003), had a 40% reduction in NTD prevalence and 46% reduction in the prevalence of spina bifida. These rates continued to decline in 2004–2007 (Table 3.1).

Other factors that may have contributed to the decline of NTDs and spina bifida, in particular after 2001, include folic acid supplementation and increased prenatal screening and diagnosis. According to the Canadian Community Health Survey, the proportion of Canadian mothers who had taken folic acid supplements in the periconceptional period increased from 47.2% to 57.8% between 2001 and 2005.[17]

FIGURE 3.1

Neural tube defect (NTD) rate, *Canada, 1996–2007*



Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1996–2007
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1996–2007. Combined rates of specific NTD categories may not add up to the total NTD rate because of rounding. *Total births include live births and stillbirths.

TABLE 3.1

Prevalence of neural tube defects and relative risks compared to 1996, *Canada, 1996–2007*

Years	Number of total births	Neural tube defects				Spina bifida			
		Cases	Rate per 10,000 total births	RR	95% CI	Cases	Rate per 10,000 total births	RR	95% CI
1996 (pre-fortification)	366,811	278	7.6	1.00		200	5.5	1.00	
1998-1999 (partial-fortification)	682,230	390	5.7	0.75	(0.68–0.83)	278	4.1	0.75	(0.66–0.84)
2001-2003 (post-fortification)	1,006,779	461	4.6	0.60	(0.55–0.66)	301	2.9	0.53	(0.49–0.61)
2004-2007 (post-fortification)	1,419,505	569	4.0	0.52	(0.49–0.57)	378	2.6	0.49	(0.44–0.54)

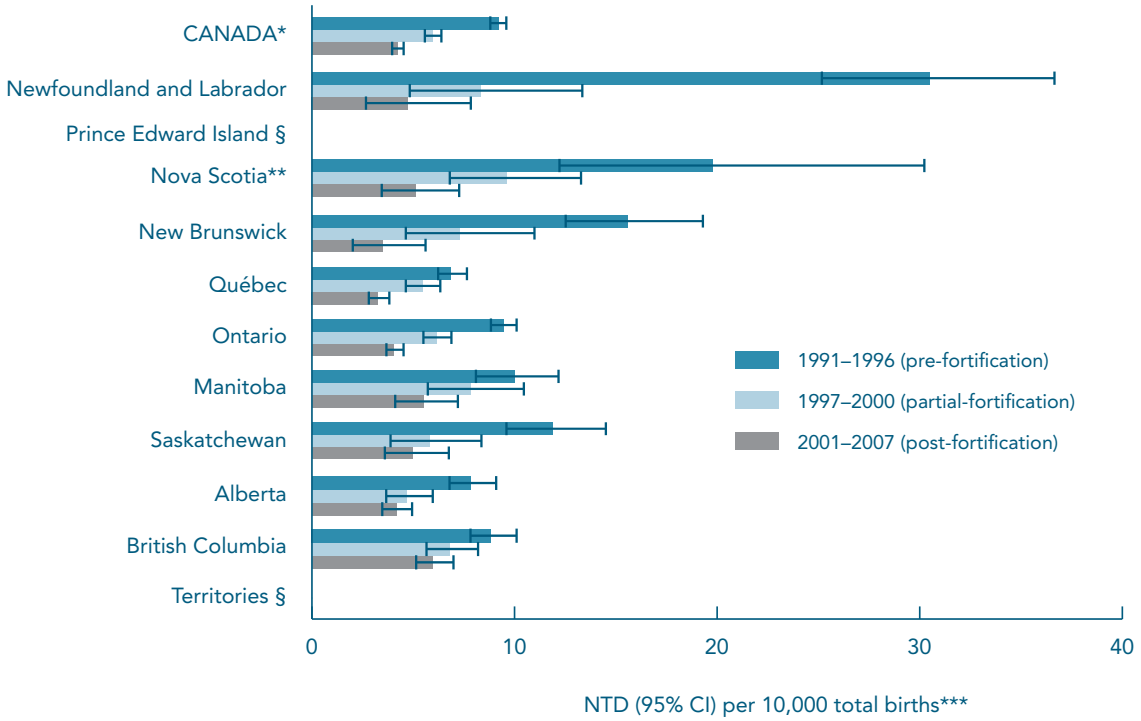
Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1996–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1996–2007.
RR—Relative Risk, CI—Confidence Interval

PROVINCIAL AND TERRITORIAL PREVALENCE RATES

The analysis of provincial and territorial rates shows that the decline in NTDs between 1998 and 2007 occurred across the country (Figure 3.2). The significant differences that existed between provinces prior to folic acid fortification were greatly diminished after fortification. In 1991–1996, the ratio of the highest to the lowest prevalence (Newfoundland and Labrador to Québec) was 4.5. In 2001–2007, the ratio of highest to lowest prevalence (British Columbia to Québec) was only 1.8 (Figure 3.2).

FIGURE 3.2

Neural tube defect (NTD) rate, by province/territory and time period, *Canada, 1991–2007 combined*



Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1991–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1991–2007.
*Territorial data was unavailable because Nunavut was not established as a territory until 1999. Data on births in Nunavut were included within those of the Northwest Territories.
**Nova Scotia data from 1991–1995 were excluded as they were not available to CCASS prior to 1996. Nova Scotia data are for 1996–2007.
***Total births include live births and stillbirths. § Rate suppressed due to small cell numbers (<5). CI—Confidence Interval

DATA LIMITATIONS

For provinces and territories other than Alberta, the primary data source for CCASS is the hospital discharge database. In Québec, an analysis of the validity of hospital discharge summaries for the identification of NTDs showed that this source has a sensitivity of 92%, but a low predictive value due to coding errors.[18] Indeed, as mentioned earlier, the rates measured by CCASS are much lower than those measured by other researchers during the same period,[14] which indicates that CCASS is not capturing all cases, leading to an underestimation of rates. Moreover, comparison of provincial rates between CCASS and De Wals et al. showed that, while rates from CCASS data are consistently lower, the under-reporting varies between provinces, therefore comparisons between jurisdictions should be interpreted with caution. Finally, a large proportion of terminations of NTD-affected pregnancies occur at a stage when stillbirth registration is not required (i.e., gestational age <20 weeks and weight <500 g).[19]

INTERNATIONAL COMPARISONS

In the United States, the birth prevalence of spina bifida was determined separately for Hispanic, non-Hispanic white people, and black people. In these three subpopulations, the respective birth prevalence rates of spina bifida were 6.5, 5.1, and 3.6 per 10,000 births in the pre-fortification period (January 1995 – December 1996) and 4.2, 3.4 and 2.9 per 10,000 births in the mandatory fortification period (October 1998 – December 2002).[20] The order of magnitude of these rates, as well as the trends associated with folic acid fortification in enriched grain products, are similar to those found

in Canada. Much higher rates have been observed in Europe in the absence of folic acid fortification in food. In the European Union, the birth prevalence of NTDs decreased from 10.5 per 10,000 total births in 2004 to 9.4 per 10,000 total births in 2008;[21] in England and Wales, the birth prevalence of NTDs has remained stable and ranged between 14 and 18 per 10,000 total births in 1995–2004;[22] and in Sweden, the birth prevalence of spina bifida has decreased from 5.5 per 10,000 in 1988-1992 to 4.4 per 10,000 births in 1993–1998 and 2.9 per 10,000 in 1999–2003, largely due to prenatal diagnosis and termination of pregnancy.[23]

TABLE 3.2

Birth prevalence of neural tube defects (NTDs) in USA and Europe

Country / Reference	Condition	Population	Period	Folic acid fortification	Prevalence (per 10,000 total births)
USA[20]	Spina bifida	Hispanic	01/1995–12/1996	None	6.5
			01/1997–09/1998	Optional	5.5
			10/1998–12/2002	Mandatory	4.2
		Non-Hispanic white	01/1995–12/1996	None	5.1
			01/1997–09/1998	Optional	4.4
			10/1998–12/2002	Mandatory	3.4
		Non-Hispanic black	01/1995–12/1996	None	3.6
			01/1997–09/1998	Optional	2.5
			10/1998–12/2002	Mandatory	2.9
	Anencephaly	Hispanic	01/1995–12/1996	None	3.9
			01/1997–09/1998	Optional	3.6
			10/1998–12/2002	Mandatory	2.8
		Non-Hispanic white	01/1995–12/1996	None	2.8
			01/1997–09/1998	Optional	2.1
			10/1998–12/2002	Mandatory	2.0
		Non-Hispanic black	01/1995–12/1996	None	2.0
			01/1997–09/1998	Optional	1.8
			10/1998–12/2002	Mandatory	1.8
Europe[21]	All NTDs		2004	None	10.5
			2008	None	9.4
England and Wales[22]	All NTDs		1995-1999		15.5
			2000-2004		16.3
Sweden[23]	Spina bifida		1993-1998	None	4.4
			1999-2003	None	2.9

IMPACT OF PRENATAL DIAGNOSIS ON BIRTH PREVALENCE

All cases of anencephaly and a large proportion of major spina bifida cases can be detected with prenatal ultrasound at 18–20 weeks. However, it is not possible to measure the impact of prenatal diagnosis and subsequent termination of affected pregnancies from CCASS data because only those terminations taking place in or after the 20th week of pregnancy, which are registered as stillbirths, are included in the dataset. Nonetheless, a study in British Columbia showed that 72.6% of pregnant women chose to terminate their pregnancy following a prenatal diagnosis of NTDs.[19]

PREVENTIVE MEASURES

Optimal folate status for all women of child bearing age has been postulated to reduce the risk of NTDs by as much as 70%. Folic acid supplementation is especially important in women with a personal and family history of NTDs as they have the highest risk.[24] It may also preferentially benefit those with other risk factors such as polymorphisms in a variety of genes involved in folate metabolism[25] (e.g., the C677T variant in the 5,10-methylenetetrahydrofolate reductase gene).[26] This includes those women on medications that impair folate metabolism such as certain anticonvulsants,[27] since they are also at increased risk for NTDs. As it is not feasible on a population basis to identify all women who may be inadequately protected against folate sensitive NTDs, daily low dose (0.4 mg/day) supplementation is recommended for all women of child bearing potential.[28]

SUMMARY

The rate of NTDs declined between 1996 and 2007. This decline is due to the introduction of folic acid fortification in certain grain products, to an increasing use of folic acid supplements among women of child bearing age, and to an increase in prenatal screening and diagnosis leading to termination of affected pregnancies. The relative contribution of these factors cannot be determined with precision.

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CHAPTER 4

CONGENITAL HEART DEFECTS

KS Joseph
Shiliang Liu

INTRODUCTION

Congenital heart defects (CHDs) are defined as "gross structural abnormalities of the heart or intra-thoracic vessels that are actually or potentially of functional significance".[1] They constitute the most common congenital anomaly among newborns, with a birth prevalence ranging from 50 to 150 per 10,000 total births.[2,3] CHDs remain one of the most important causes of infant morbidity and mortality and also constitute an important cause of disability and death in youth and adult life.[4] Although various potentially modifiable and non-modifiable risk factors for CHDs have been identified in recent years, it is unclear if awareness of risk factors has resulted in a change in the frequency of such malformations. For instance, one study[5] from Québec showed a decline in the birth prevalence of severe CHDs from 1998 to 2005 (following the introduction of food fortification with folic acid). However, another study from Northern England,[6] where food is not fortified with folic acid, documented a substantial increase in such defects.

RISK FACTORS

There is a large body of evidence on the genetic and non-genetic risk factors for CHDs.[7,8] The genetic causes of CHDs include chromosomal syndromes and single gene disorders. Down syndrome is associated with congenital heart disease in approximately 45% of cases, although no single gene on chromosome 21 has yet been identified as responsible for heart defects.[9] DiGeorge syndrome (typically characterized by 22q11 deletion) and Williams-Beuren syndrome (typically characterized by a 7q11.23 microdeletion) are other examples of chromosomal disorders, while Alagille syndrome (commonly caused by mutations of the gene JAG1), Noonan syndrome (due to mutations in PTPN11, SOS1, or KRAS), and Holt-Oram syndrome (with mutations in TBX5) are examples of single gene defects.[7] Family history of CHDs sometimes helps in the prenatal identification of such heritable defects.

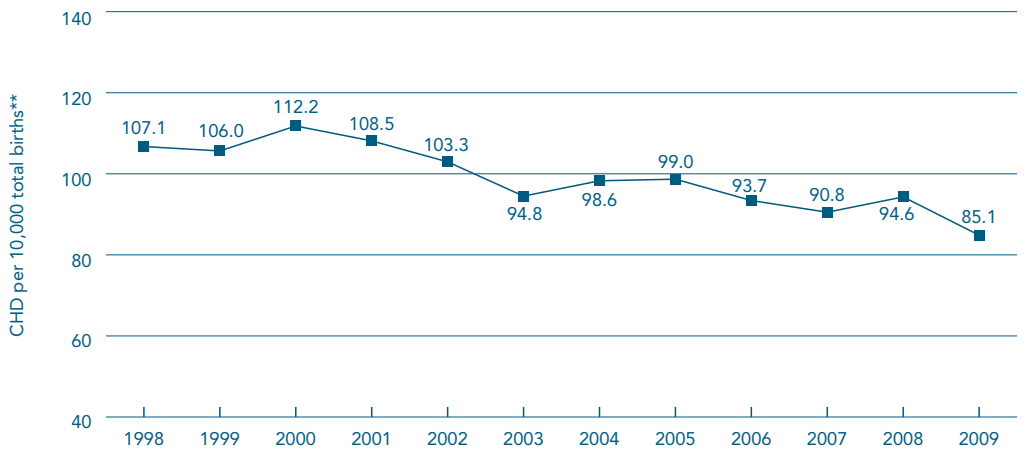
Recent studies have also implicated various modifiable non-inherited risk factors,[8] though the evidence is less consistent in some instances and more definitive in others. Modifiable determinants of CHDs include maternal rubella during pregnancy, use of multivitamin/folic acid supplements, medications (e.g., anti-epileptics, thalidomide, isotretinoin and lithium), glycemic control for diabetes mellitus and dietary modification for maternal phenylketonuria. Other possible causes include maternal illnesses (e.g., influenza, HIV infection, and systemic lupus erythematosus), therapeutic drug exposure (e.g., anti-virals and antifungal agents), non-therapeutic drug exposure (e.g., cocaine, marijuana and cigarette smoking), environmental exposures (e.g., organic solvents, herbicides, and pesticides) and socio-demographic and lifestyle characteristics (e.g., race/ethnicity and maternal age). Paternal determinants such as age and cocaine, or marijuana use have also been implicated as potential causes.[8]

PREVALENCE RATE OF CONGENITAL HEART DEFECTS IN CANADA

Estimates of the prevalence of CHDs in Canada vary somewhat depending on the data source used to ascertain rates. Canadian Congenital Anomalies Surveillance System (CCASS) data using Discharge Abstract Data (DAD) provide the most recent information and show that rates of CHDs (as ascertained up to 30 days of age) decreased by 21% from 107.1 per 10,000 total births in 1998 to 85.1 per 10,000 total births in 2009 (Figure 4.1).

FIGURE 4.1

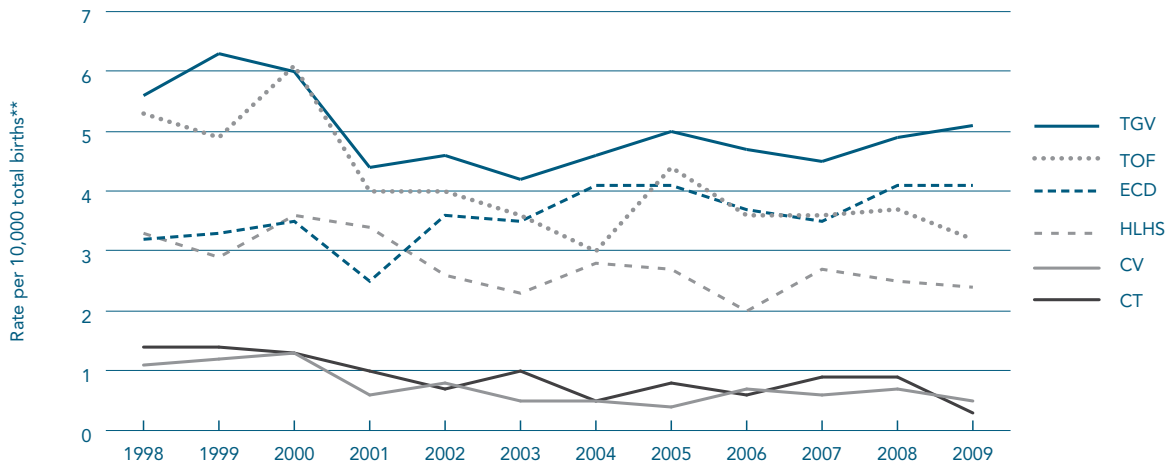
Congenital heart defect (CHD) rate, *Canada (excluding Québec),* 1998–2009*



Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2009.
Note: Data quality issues pertaining to these birth prevalence estimates are discussed in the text.
*Québec was excluded because data were not available for all years. **Total births include live births and stillbirths.

FIGURE 4.2

Rate of selected congenital heart defects (CHDs), *Canada (excluding Québec),* 1998–2009*



CT: Common truncus (P value for trend <0.0001)
TGV: Transposition of great vessels (P value for trend <0.05)
TOF: Tetralogy of Fallot (P value for trend <0.0001)
CV: Common ventricle (P value for trend <0.0001)
ECD: Endocardial cushion defects (P value for trend <0.05)
HLHS: Hypoplastic left heart syndrome (P value for trend <0.001)
Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2009.
*Québec was excluded because data were not available for all years. **Total births include live births and stillbirths.

Figure 4.2 shows the birth prevalence rates of selected CHDs in Canada (excluding Québec) between 1998 and 2009. Rates of common truncus, tetralogy of Fallot and common ventricle showed a decrease in frequency between 1998 and 2007, whereas rates of transposition of the great vessels were stable and endocardial cushion defects increased.

Table 4.1 shows rates of some specific CHDs as estimated by the CCASS and the Alberta Congenital Anomalies Surveillance System (ACASS) and provides some insight into how different data collection methods affect rates (even if estimates apply to different regions and different periods). Rates of common truncus, endocardial cushion defects and hypoplastic left heart syndrome were not significantly different in Alberta, 2000–2009, as estimated by ACASS, and Canada (excluding Québec), 1998–2009 as estimated by CCASS. However, the approximately similar frequency of CHDs in the different databases does not necessarily imply equal accuracy of case identification or case-by-case correspondence between the different databases. The two data sources have the following features:

1. The inclusion of information from pregnancy terminations, use of rigorous case definitions, hierarchical classification and standard data verification procedures makes ACASS data the most accurate information on CHDs in Canada.
2. Underestimation of cases in CCASS is likely offset by overestimation due to coding problems (e.g., tetralogy of Fallot coded as both the tetralogy and as a ventricular septal defect) and lack of data verification. For instance, infants with patent ductus arteriosus and patent foramen ovale who are <37 weeks gestation or <2,500 g birth weight may be coded as cases in CCASS, while in ACASS such cases are only coded in full term infants.

TABLE 4.1

Rates of specific congenital heart defects,* *Alberta and Canada (excluding Québec), 2000–2009 and 1998–2009*

Diagnostic category	Rate (95% CI) in Alberta 2000–2009	Rate (95% CI) in Canada 1998–2009
Common truncus	0.6 (0.4–0.9)	0.9 (0.8–1.0)
Transposition of great vessels	3.5 (3.0–4.1)	5.0 (4.8–5.2)
Tetralogy of Fallot	3.4 (2.9–4.0)	4.1 (3.9–4.3)
Ventricular septal defect	31.2 (29.5–32.9)	35.0 (34.3–35.6)
Atrial septal defect	19.6 (18.3–21.0)	46.9 (46.1–47.6)
Endocardial cushion defect	4.5 (3.9–5.2)	3.6 (3.4–3.8)
Hypoplastic left heart syndrome	3.1 (2.6–3.7)	2.8 (2.6–3.0)

Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 2000–2009.
Source of Canadian data: Canadian Congenital Anomalies Surveillance System, 1998–2009; and the Canadian Institute for Health Information, 1998–2009.
Note: Data quality issues pertaining to these prevalence estimates are discussed in the text.
*Per 10,000 total births. Total births include live births and stillbirths. CI—Confidence Interval

TABLE 4.2

Congenital heart defect (CHD) international rates, by region/country, *2000-2005 combined*

Country/Region	Rate of CHDs*
Styria, Austria	153.4
Hainaut, Belgium	66.6
Zagreb, Croatia	53.9
Odense, Denmark	89.1
Paris, France	83.8
Mainz, Germany	119.0
Emilia Romagna, Italy	68.6
Malta	152.5
Northern, Netherlands	60.8
Norway	102.7
Ukraine	77.8

Source: Special Report: Congenital Heart Defects in Europe, 2000-2005 EUROCAT 2009.[3]
*Rate numerators include CHDs among live births, fetal deaths and terminations of pregnancy and; rates are expressed per 10,000 total births (live births plus fetal deaths).

TABLE 4.3

Prevalence of specific subtypes of non-chromosomal congenital heart defects, EUROCAT Registry, *2000–2005*

Diagnostic category	Prevalence per 10,000 total births*
Common truncus	0.9
Transposition of great vessels	3.5
Tetralogy of Fallot	2.8
Ventricular septal defect	30.6
Atrial septal defect	20.5
Hypoplastic left heart syndrome	2.6

Source: Special Report: Congenital Heart Defects in Europe, 2000-2005 EUROCAT, 2009.[3]
*Rate numerators include CHDs among live births, fetal deaths and terminations of pregnancy and; rates are expressed per 10,000 total births (live births plus fetal deaths).

PROVINCIAL AND TERRITORIAL PREVALENCE RATES

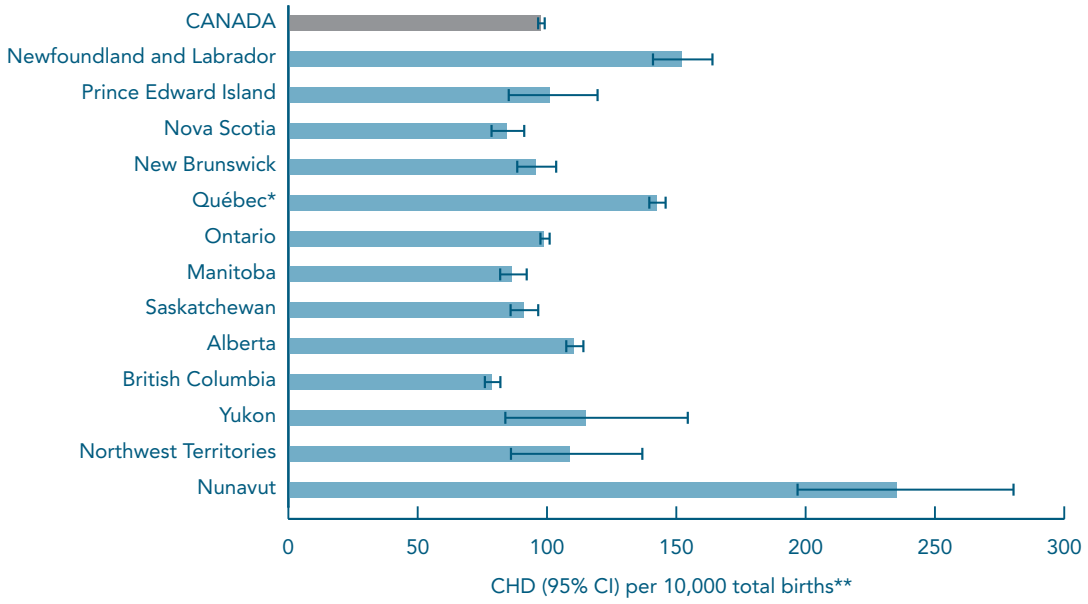
Figure 4.3A shows birth prevalence rates of CHDs in each province and territory for 2000–2009 based on the DAD (estimate for Québec, 1998–2007, based on MED-ÉCHO). Rates of CHDs in Newfoundland and Labrador, Québec, Alberta and Nunavut were higher than the Canadian average while rates in Nova Scotia, New Brunswick, Manitoba, Saskatchewan and British Columbia were lower (Figure 4.3B). These differences in prevalence rates could represent true differences in rates of CHDs or differences in case identification (diagnosis) during the birth hospitalization. True differences in rates may arise from population differences in genetic and other risk factors or differences in the availability and uptake of prenatal diagnosis and subsequent pregnancy terminations prior to 20 weeks gestation.

INTERNATIONAL COMPARISONS

Table 4.2 shows rates of CHDs in several European registries in 2000–05.[3] Birth prevalence ranged from 53.9 per 10,000 total births in Croatia to 153.4 per 10,000 total births in Austria. Registries included live births, stillbirths and terminations of pregnancy; however, terminations did not occur in some countries, but were frequent in others e.g., France. Table 4.3 shows the birth prevalence of specific congenital heart defect subtypes; rates were similar to those documented in Canada, especially rates estimated by ACASS that also capture terminations (Table 4.1).

FIGURE 4.3A

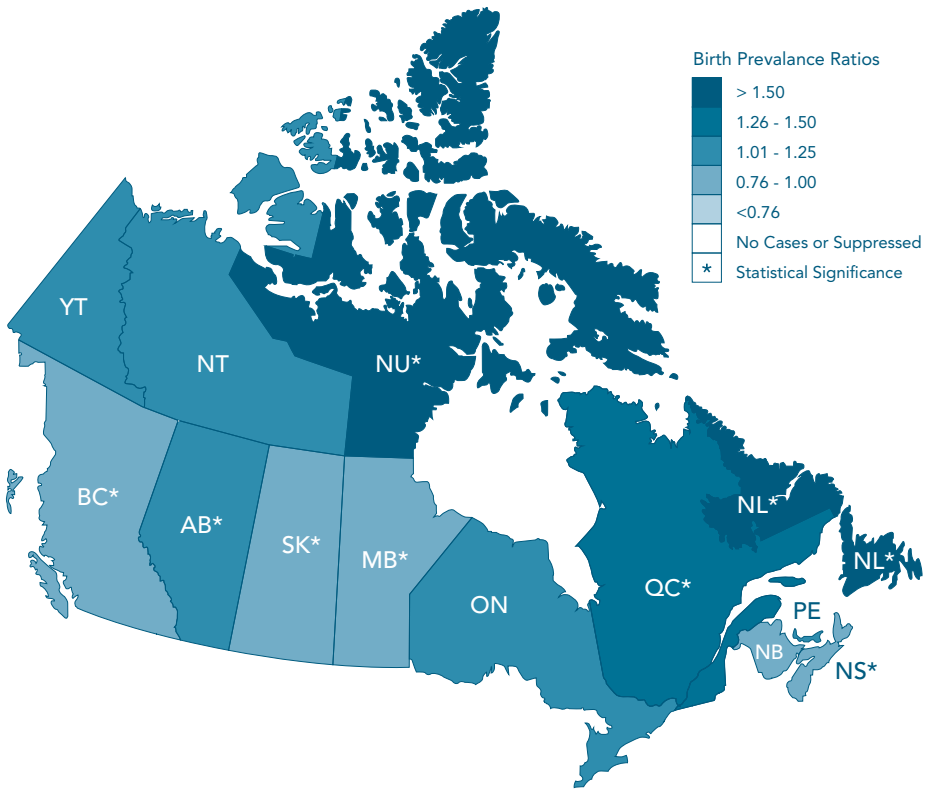
Congenital heart defect (CHD) rate, by province/territory, *Canada, 2000–2009 (Quèbec 1998–2007) combined*



Source: Discharge Abstract database of the Canadian Institute for Health Information, 2011.
Source for Québec: Estimated from the Canadian Congenital Anomalies Surveillance System database, 1998–2007.
*Québec data shows the combined rate for the 10-year period 1998–2007.
**Data quality issues pertaining to these birth prevalence estimates are discussed in the text. Total births include live births and stillbirths.
CI—Confidence Interval

FIGURE 4.3B

Ratio of provincial/territorial congenital heart defect rate to national rate,**
Canada, 2000–2009, (Québec 1998–2007) combined



Source: Canadian Congenital Anomalies Surveillance System database, 1998–2009 (Québec 1998–2007).
**This ratio calculates the birth prevalence rate per 10,000 total births of each individual province/territory to the birth prevalence rate for Canada during the specified time period. The birth prevalence for Canada includes cases for which province/territory is unknown.

IMPACT OF PRENATAL DIAGNOSIS ON BIRTH PREVALENCE OF CONGENITAL HEART DEFECTS

It is unclear if the live birth prevalence of CHDs has declined in recent years as prenatal diagnosis of such conditions has improved.[5,6] However, Canadian studies[10,11] have shown that congenital anomaly-related fetal deaths have increased at very early gestation and declined at late gestation, and congenital anomaly-related infant deaths have decreased in recent decades. Between 1981–85 and 1994–98, CHDs related fetal deaths at 20-25 weeks gestation increased from 0.02 to 0.3 per 10,000 fetuses at risk,* CHDs related fetal deaths at 26–44 weeks decreased from 0.5 to 0.4 per 10,000 fetuses at risk and CHDs related infant deaths decreased from 10.2 to 5.6 per 10,000 live births.[11] The change in congenital anomaly-related fetal death rates is likely an effect of prenatal diagnosis and pregnancy termination, whereas the decline in congenital anomaly-related infant deaths probably represents the combined effect of prenatal diagnosis and pregnancy termination and improvements in the postnatal management of CHDs.

* The fetuses at risk model estimates gestational age-specific stillbirth rates as an incidence, with stillbirths at any gestation in the numerator and all fetuses at risk of stillbirth in the denominator i.e., the denominator includes all live births and stillbirths that occur at the gestation of interest and beyond.

Studies show that approximately one-third of all CHDs and 60–80% of severe heart anomalies are diagnosed prenatally,[12,13] though such estimates vary across populations and will continue to increase with wider access to health services. The proportion of prenatally diagnosed cases that are terminated also varies widely, ranging from 30% to 60%.[12-15] Termination of pregnancy is more common when the heart defects are associated with chromosomal anomalies or other syndromes or with multiple anomalies. A study[16] from a single Canadian institution showed that 19% of cases of tetralogy of Fallot were diagnosed prenatally between 1998 and 2006. Of the 15% that were terminated, over half had other congenital anomalies such as omphalocele, talipes, pentalogy of Cantrell and trisomy 18. Some estimates suggest that prenatal screening and pregnancy termination has led to a 21% reduction in birth prevalence of congenital heart disease.[17,18] However, recent improvements in the management of isolated heart defects mean that parents increasingly opt for attempts at postnatal surgical correction over pregnancy termination.

PREVENTIVE MEASURES

Food fortification with folic acid and periconceptional supplementation with multivitamins are potential preventive measures.[5,8] Antenatal assessment of rubella immunoglobulin titres can identify seronegative women who could be offered immunization postnatally. The *Canadian Immunization Guide*[19] recommends that women not immunized in childhood (e.g., immigrant women from countries where rubella vaccination is not routine), should be offered one dose of mumps-measles-rubella vaccination sufficiently prior to pregnancy. Avoidance of exposures to illnesses, drugs and environmental contaminants would be advisable for women planning a pregnancy. Such avoidance can be challenging when the medication in question is strongly indicated (e.g., for psychosis or epilepsy), though alternative medication with lesser teratogenic potential may be an option. On the other hand, Health Canada recommends that medications such as isotretinoin, used for severe acne, should only be prescribed to women of reproductive age in accordance with standard guidelines.[20] A family history of CHDs disease can be used for referral to a genetic counsellor and may facilitate the early prenatal detection of cases. Finally, prenatal diagnosis and the option and availability of termination of pregnancies for severe CHDs can reduce the birth prevalence, if identified early in gestation.

SUMMARY

CHDs are important congenital anomalies, in terms of both frequency and the severity of associated morbidity. The birth prevalence of CHDs in Canada has declined by about 18% in recent years. However, this finding needs to be investigated further as potential problems in contemporary data sources do not permit a robust inference. Provincial and territorial rates show wide variation in birth prevalence, although the significance of observed differences is not entirely clear. International comparisons show that rates of CHDs in Canada are similar to those in European countries.

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CHAPTER 5

OROFACIAL CLEFTS

Julian Little
Chantal Nelson

INTRODUCTION

Every year, approximately 600 babies are born with orofacial clefts (OFCs) in Canada.[1] Affected children need multidisciplinary surgical and nonsurgical care from birth until adulthood and they and their families may suffer psychological effects.[2] Increased perinatal mortality has been observed even in the absence of associated anomalies and the risk of death remains higher than expected throughout childhood and adulthood.[3] The causes of OFCs remain largely unknown; therefore, in the absence of information on which to base primary prevention strategies, these congenital anomalies (CA) continue to pose major challenges in terms of morbidity, health care, and social and employment exclusion for affected individuals, their families and society.[1]

On the basis of their distinct developmental origins, and the observation that under most circumstances cleft lip with or without cleft primary palate (CL±CP) and isolated cleft secondary palate (CP) do not segregate in the same family, OFCs are usually subdivided into these two categories (primary and secondary).[2] Disruption in any of the processes of cell proliferation, migration, adhesion, differentiation and apoptosis involved in the highly coordinated growth and fusion of the facial processes and palatal shelves before the end of the sixth week of development can result in clefts of the lip and primary palate; between the sixth and tenth weeks, they cause clefts of the secondary palate.

PREVALENCE RATE OF OROFACIAL CLEFTS IN CANADA

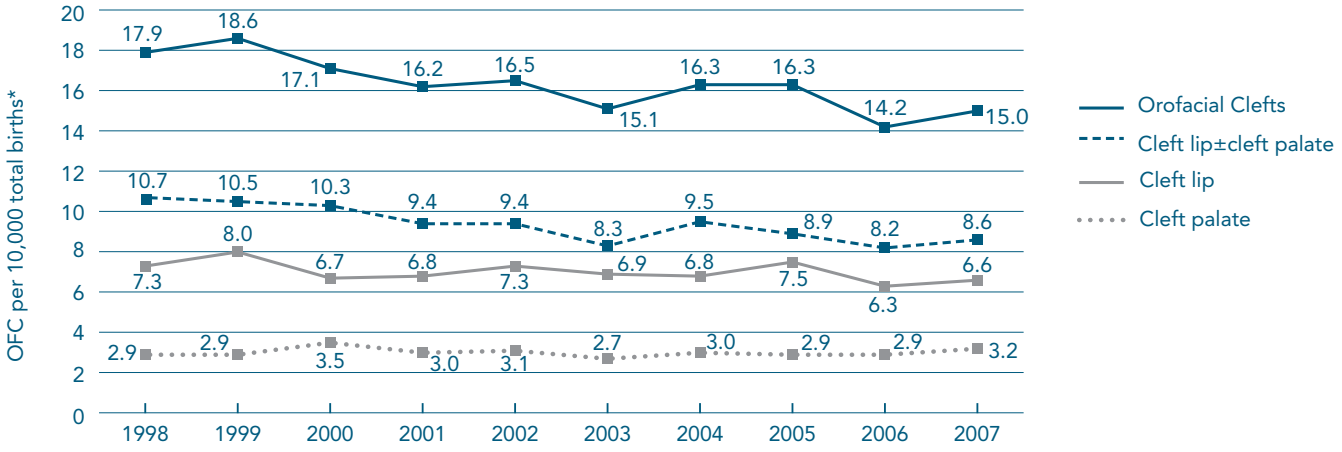
The overall prevalence at birth of OFCs in Canada from 1998–2007 was 16.3 per 10,000 total births (live births and stillbirths). The prevalence at birth of CL±CP was 9.4 per 10,000 and of CP 7.0 per 10,000. There appeared to be a small decline in the prevalence at birth of OFCs but not CP (Figure 5.1). Of a total of 5,599 births with OFCs, 95 were stillborn of which 70 had an additional anomaly. The majority of babies born with orofacial clefts do not have additional anomalies, but the precise ratio of isolated to complex cases cannot be determined from CCASS data alone.

PROVINCIAL AND TERRITORIAL PREVALENCE RATES

There is marked variation in the prevalence of OFCs at birth in Canada (Figures 5.2A and B). For the overall period 1998 to 2007, the rates ranged from 14.1 (95% CI: 11.5–17.2) per 10,000 in New Brunswick to 38.2 (95% CI: 21.8–62.1) per 10,000 in Nunavut. However, the high extreme of this distribution was from Nunavut where the number of births was less than 5,000. In jurisdictions with over 10,000 births, the variation was less pronounced.

FIGURE 5.1

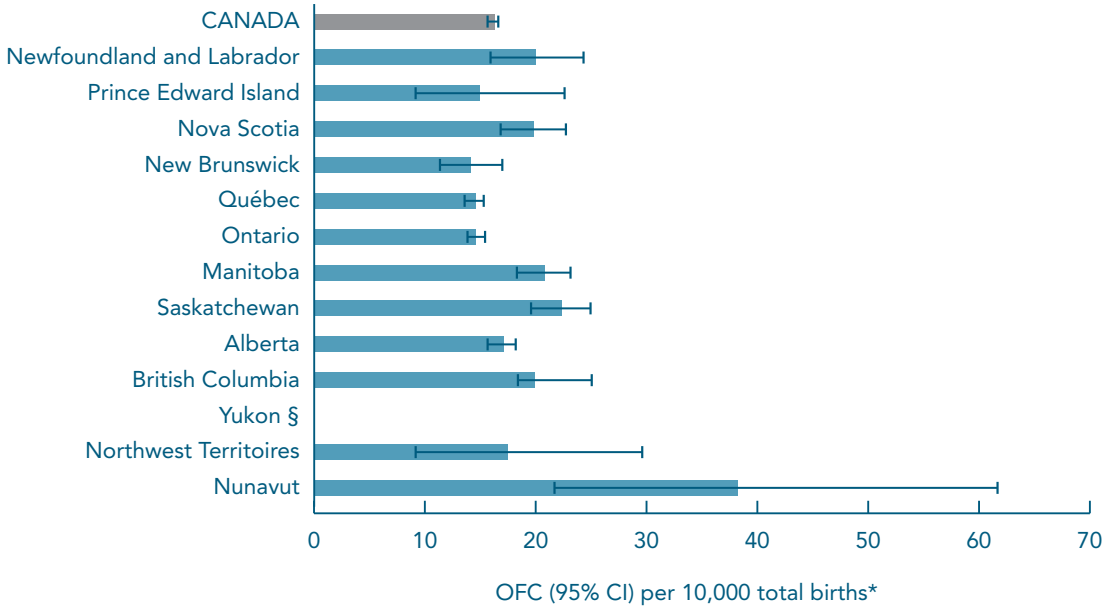
Total orofacial cleft (OFC) rate, *Canada, 1998–2007*



Source: Public Health Agency of Canada, Canadian Congenital Anomalies Surveillance System, 1998–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1998–2007.
Note: Rates that do not add up exactly may be due to rounding.
*Total births include live births and stillbirths.

FIGURE 5.2A

Orofacial cleft (OFC) rate, by province/territory, *Canada, 1998–2007 combined*



Source: Public Health Agency of Canada, Canadian Congenital Anomalies Surveillance System, 1998–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1998–2007.
*Total births include live births and stillbirths. § Rate suppressed due to small cell numbers (<5). CI—Confidence Interval

INTERNATIONAL COMPARISONS

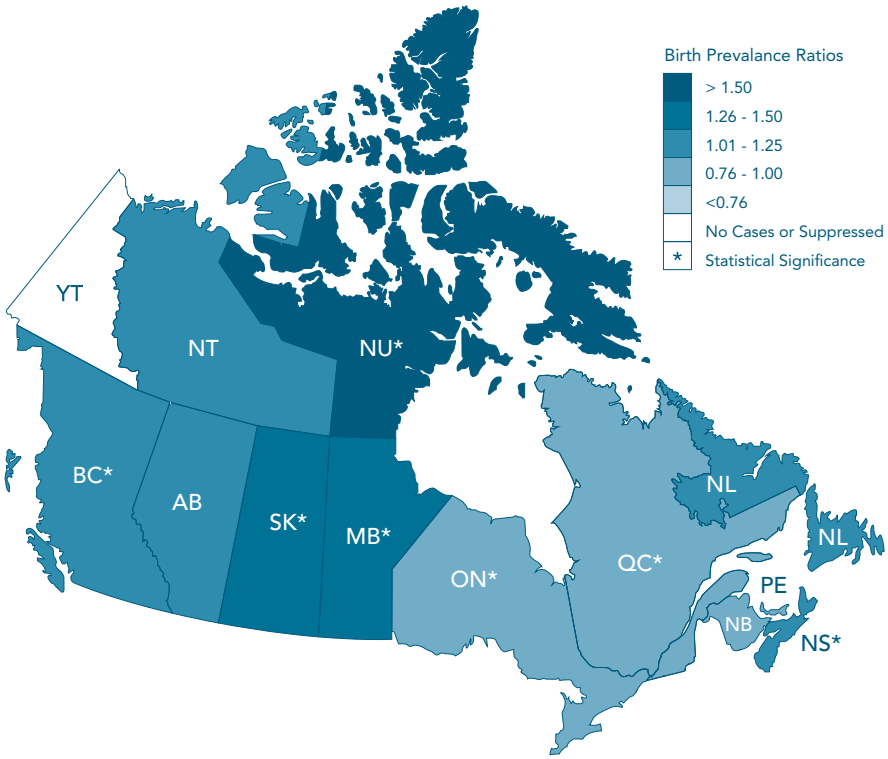
A review of peer-reviewed literature and supplemental data obtained from the European Surveillance of Congenital Anomalies (EUROCAT) and the National Birth Defects Prevention Network (NBDPN, USA) registries found that, from 1958–1998, there was approximately an eightfold variation in the prevalence at birth of CL±CP with a range from 0.3 (USA) to 2.3 (India) per 1,000 births internationally.[4] This is consistent with 2000–2005 data from registries in 30 countries during the period which also suggested about an eightfold variation of CL±CP in birth prevalence.[5] Numerous methodological issues affect the comparability of published data from different jurisdictions including the source population of births considered, the length of data collection, types and numbers of sources of ascertainment, inclusion/exclusion criteria, clinical classification and sampling fluctuation.[5] Moreover, little or no information on the frequency of OFCs is available for many parts of the world, notably parts of Africa, Asia and Eastern Europe. See Table 5.1 for a list of selected international comparisons.

IMPACT OF PRENATAL DIAGNOSIS ON BIRTH PREVALENCE OF OROFACIAL CLEFTS

According to 2000–2005 data from registries that record terminations of pregnancy, the proportion of cases of CL±CP accounted for by fetuses from terminated pregnancies was less than 5%.[5] In the National Birth Defects Prevention Study, US, which included OFCs cases without chromosomal abnormalities or single gene disorders in live births, stillbirths and pregnancy terminations, the proportions of prenatally diagnosed cases were 33.3% for cleft lip with cleft palate, 20.3% for cleft lip alone and 0.3% for cleft palate alone.[6] Prenatal detection rates are higher for OFCs associated with malformations in other systems than for isolated clefts,[7] and terminations of pregnancy are more common when the cleft is associated with other anomalies.[8]

FIGURE 5.2B

Ratio of provincial/territorial orofacial cleft rate to national rate,** *Canada, 1998–2007 combined*



Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1998–2007.
**This ratio calculates the birth prevalence rate per 10,000 total births of each individual province/territory to the birth prevalence rate for Canada during the specified time period. The birth prevalence for Canada includes cases for which province/territory is unknown.

TABLE 5.1

Cleft lip with or without cleft palate international rate,* by region/country, *2007*

Country/Region	Rate of cleft lip with or without cleft palate (CL±CP)	Rate of cleft palate (CP)
CANADA†	8.6	6.6
Alberta, Canada	16.6	5.3
Atlanta, USA	8.6	3.5
Texas, USA	11.0	5.2
Utah, USA	12.3	7.6
Victoria, Australia	11.9	5.4
Western Australia	12.6	7.0
Hungary	9.0	4.1
Japan	21.2	4.5
Norway	13.1	6.2
South America	14.5	4.0
Wales, UK	12.7	9.0
Finland	11.9	12.1
Strasbourg, France	8.5	7.6
Emilia Romagna, Italy	5.9	6.6

Source: International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) Annual Report, 2009 (data from 2007).
†Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 2007.
*Per 10,000 total births.

RISK FACTORS

Approximately 70% of cases of CL±CP and 50% of cases of CP are considered to be multifactorial, i.e., due to the interaction of genetic predisposition and environmental factors.[9] The remaining cases have syndromes associated with known teratogens, chromosomal anomalies or one of over 500 single gene syndromes.[9] For isolated cases, there is debate about the effects of the anatomical severity of the cleft in the index child on the recurrence risk in first-degree relatives.[10] As would be expected for a multifactorial condition, a large Danish study showed that the recurrence risk declined sharply by degree of relationship: 2.7%–3.5% (depending on the type of defect in the index case) for first-degree, 0.7%–0.8% for second-degree and 0.3%–0.6% for third-degree relatives.[11] Little information is available on ethnic differences in cleft frequency in Canada, but Aboriginal populations may be at increased risk.[12,13]

In Greater Glasgow (Scotland) in 1974–1985, the highest rates of OFCs were observed in areas with high proportions of local authority (public) housing, high unemployment and a preponderance of unskilled workers, whereas the lowest rates were found in affluent areas with high proportions of professional and non-manual workers with largely owner occupied or high-quality housing.[14] Similar findings have been reported in other parts of the UK.[1] Variation by ethnic group may also reflect socioeconomic status SES differences. Maternal smoking during pregnancy has been linked consistently with increased risk of both CL±CP and CP,[15] with a population-attributable risk as high as 20%,[16] Moreover, the impact of tobacco may have been underestimated because maternal exposure to environmental tobacco smoke (passive smoking), which some studies suggest is positively associated with OFCs,[17] has not been assessed in most investigations.

While some studies suggest that heavy maternal alcohol consumption during early pregnancy increases the risk of OFCs, the evidence as to the effects of moderate maternal alcohol use is inconsistent.[1]

Both maternal obesity[18] and underweightedness[19] have been found to be associated with CL±CP. In a meta-analysis of observational studies, maternal use of multivitamin supplements in early pregnancy was associated with a decreased risk of OFCs, but with heterogeneity between studies.[20] The combined effect estimates indicated risk reductions of 25% and 12% for CL±CP and CP respectively.[20] It is not possible to determine from these studies which of the nutrients in the multivitamins are protective and whether or not other healthy behaviours of multivitamin users confound these results. Similarly, the effect of dietary or supplemental intake of folic acid on OFCs is uncertain. In North America, where there has been mandatory fortification of grains with folic acid since November 1998, there is some evidence of a subsequent decline in the prevalence at birth of CL±CP.[21] For all clefts combined, there was a decrease after the introduction of fortification in the United States, but not in Canada, Argentina, Brazil or Chile.[21] Additional risk factors are presented in Table 5.2.

TABLE 5.2

Additional risk factors for orofacial clefts (OFCs)

Vitamin deficiencies	Lower vitamin B-6 (pyridoxine and related compounds)[22] and zinc levels[23] have been associated with an increased risk of OFCs.
Medication use	Certain anti-convulsant medications, notably diazepam, phenytoin and phenobarbital[24] and possibly lamotrigene[25] increase the risk of OFCs. Valproic acid monotherapy was associated with an increased risk of CP,[26] but carbamazepine did not appear to increase the risk of CL±CP.[27] Infection and febrile illness in early pregnancy may increase the risk of a cleft.[28] Reported use of acetaminophen in the first trimester, other than in combination products, was not associated with OFCs, and appeared to reduce the risk of CL±CP in women who reported concomitant febrile illness.[29]
Occupational and environmental exposures	Maternal occupational exposures to organic solvents,[30] maternal exposure to ambient air pollutants[31] and parental exposure to agricultural chemicals[32] have been inconsistently associated with OFCs.
Gene-environment interactions	Although many potential gene-environment interactions in the etiology of OFCs have been investigated,[33] results have been inconclusive.[2]

PREVENTIVE MEASURES

Identification of modifiable risk factors is the first step towards primary prevention. Modifiable risk factors include smoking tobacco and obesity, as both are consistently associated with OFCs.

Multivitamin supplements are associated with a reduced risk for CL±CP and perhaps CP. There are reported adverse effects of prolonged use of supplements containing antioxidant vitamins and it is important to clarify the specific nutrients and/or minerals that account for this apparent inverse association.[2]

With regard to tertiary prevention, OFCs have health consequences in the longer term that are not directly related to the presence of the cleft and the interventions used to manage it. There is a need not only for surveillance of the occurrence of OFCs, but also of later effects, with a view to maximizing the effectiveness of both primary prevention efforts and therapeutic interventions.

SUMMARY

OFCs continue to be an important cause of morbidity among Canadian children. Evidence is increasing that smoking and obesity increase risk of occurrence, which reinforces the need to strengthen public health efforts relating to reduction of these factors. Multivitamin supplementation is associated with reduced risk of CL±CP and perhaps CP, but there is a need for better understanding of this relationship in order to inform primary prevention efforts. The development of enhanced surveillance of CL±CP and CP, together with focused inter-disciplinary research, is required to identify additional modifiable risk factors. In addition, surveillance of outcomes for children with OFCs will be important in terms of maximizing the success of tertiary prevention efforts.

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CHAPTER 6

LIMB DEFICIENCY DEFECTS

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INTRODUCTION

Limb Deficiency Defects (LDDs), also known as limb reduction defects, are conspicuous anomalies that are highly variable in their presentation. They can be characterized by total or partial absence of a limb, or can involve a smaller portion, such as a missing finger or toe.[1] LDDs can occur as isolated malformations or be found in association with other anomalies. Although they are relatively uncommon, the surveillance of these anomalies is important as their occurrence can contribute to the identification of teratogens. Indeed, surveillance of congenital anomalies in many jurisdictions was introduced following the identification of the embryopathy associated with thalidomide exposure in the late 1950s and early 1960s.

LDDs are a heterogeneous group of limb malformations. Three to eight infants per 10,000 live births are affected with an LDD[1-4] and in at least 30% of these the LDD is associated with other congenital malformations.[5,6] The most common cause of limb deficiency relates to vascular disruption (2.2 per 10,000),[3] although the precise pathogenetic mechanisms involved in this remain unclear. Mortality is increased when the malformation is found in association with severe anomalies of other systems, such as cardiac defects.

The most severe LDD is Amelia — absence of a limb, while partial absences are often classified based on the affected segment. Intercalary defects refer to the absence or hypoplasia of a long bone (e.g., femur or humerus) with more normal structures distally. Terminal transverse defects have absence of distal structures perpendicular to the limb. Some transverse defects can be complete (e.g., total absence of a forearm or foot or just involve certain digits).[3] Longitudinal defects are defined as the absence or hypoplasia of bones parallel to the longitudinal axis and can be characterized as central, preaxial (thumb/radial side) or postaxial (fifth ray/ulnar side) depending on the affected developmental field.

Limb development is a complex process involving multiple molecular networks. Limb differentiation occurs sequentially with the upper limb developing 24 hours before the lower and is first recognized as a small limb bud at the 26th day after fertilization.[7] There are three different axes on which the limb develops. Certain genes are necessary for limb outgrowth, (e.g., *TBX5* for the upper limb).[8]

Classifications of limb defects can be anatomic, molecular, etiological or embryologic. Swanson proposed a classification of limb malformations based on patterns of deficiencies according to the parts that have been primarily affected by certain embryological failures.[9] Although intended for use with hand changes, it can be extrapolated to include the foot and entire upper and lower limbs. Category I refers to failure of formation of parts (arrest of development) while V refers to undergrowth (hypoplasia) and VI refers to congenital constriction band syndrome (also known as amniotic band syndrome). Each general category can be further classified (e.g., Category I can be complete or partial; transverse or longitudinal). Gold and colleagues have proposed a classification based on the anatomy and etiology of the defect.[3]

Challenges in the surveillance of LDDs result from inconsistent classification systems. Definitions based on embryologic involvement have been utilized, but are not universally accepted and do not necessarily translate into the International Classification of

Diseases (ICD) codes.[10] Furthermore, the transition from ICD9 to ICD10 involved classification changes that did not capture all defects consistently (e.g., central ray deficiency/split hand-foot malformation). The International Clearinghouse for Birth Defects Surveillance and Research proposed a descriptive classification system, and distinguishes anomalies into three general types: deficiencies, supernumerary and fusion/separation defects.[11,12]

RISK FACTORS

In addition to known single gene disorders, LDDs can be due to chromosomal causes, early chorionic villous sampling[13] and other environmental insults including the medications thalidomide[14] and misoprostol.[15] Thalidomide is the most well known teratogen with respect to limb development. The critical period of sensitivity to thalidomide embryopathy is between 20 and 36 days post conception.[16] Approximately 20% of pregnancies exposed during this gestational window will result in affected children who have a wide variety of LDDs in addition to other congenital malformations.[16,17] Recently, it has been shown that infants born after in vitro fertilization show an increased risk for limb reduction defects.[18]

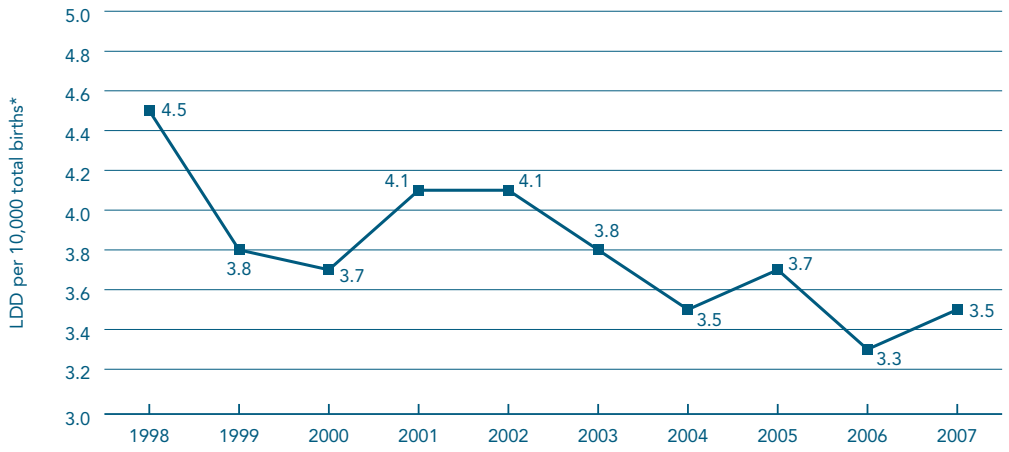
Altered homocysteine metabolism has been associated with an increased risk of neural tube defects. Maternal homozygosity for the common methylenetetrahydrofolate reductase mutation, C677T, a known contributor to neural tube defects has also been suggested as a potential risk factor for limb defects.[19] While the protective effect of folic acid for neural tube defects is well established, data with respect to LDDs is conflicting. Bower et al. showed that neither folic acid supplements nor dietary folate prevented LDDs.[20] Robitaille et al. showed that LDD rates were not associated with supplement use, but that transverse limb deficiencies were associated with low intakes of riboflavin from diet.[21] Ethnicity can also play a role. Werler and colleagues showed that Hispanic women had an increased risk for terminal limb deficiencies. These researchers also demonstrated that maternal cigarette smoking and aspirin use both increased the risk of these malformations.[22] Drug exposures associated with a potential increase risk for LDDs include valproic acid, amniopterin, methotrexate, hydantoin and isotretinoin.[17,23-25] Pregestational maternal diabetes has also been associated with limb deficiency.[26-28] Maternal obesity has been implicated as well, but the literature is inconsistent.[29-32]

PREVALENCE RATE OF LIMB DEFICIENCY DEFECTS IN CANADA

In 1998 in Canada, the rate of LDDs in live births and stillbirths (including pregnancy terminations over 20 weeks gestation occurring in hospitals) was 4.5 per 10,000 total births compared to 3.5 per 10,000 in 2007 (Figure 6.1). A decrease in risk factors, such as cigarette smoking and an increase in preventive measures, such as food fortification with folic acid, may help to explain the downward trend. However, it may also be a reflection of increased uptake of prenatal diagnosis and termination of affected pregnancies.

FIGURE 6.1

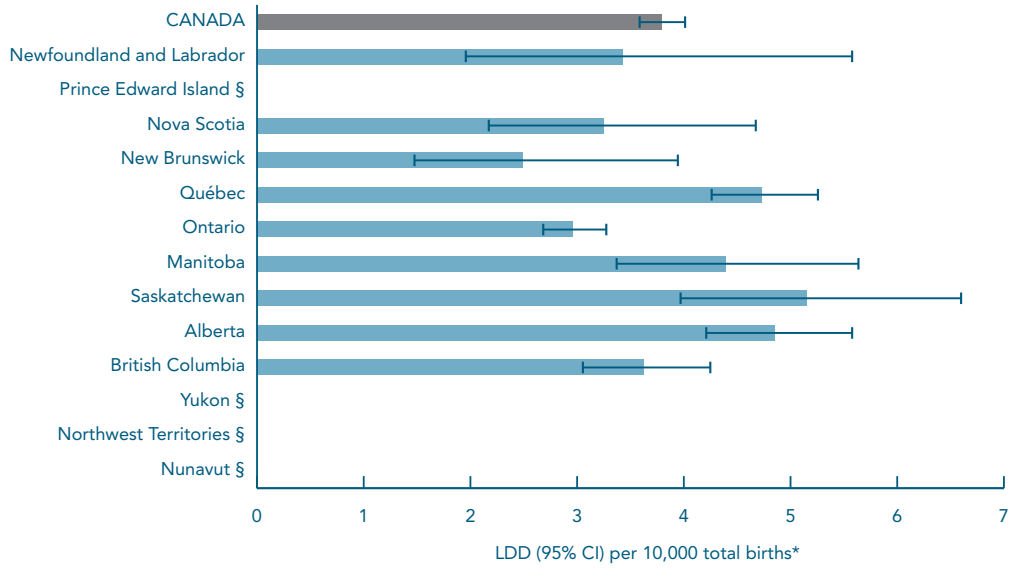
Limb deficiency defect (LDD) rate, *Canada, 1998–2007*



Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1998–2007. *Total births include live births and stillbirths.

FIGURE 6.2A

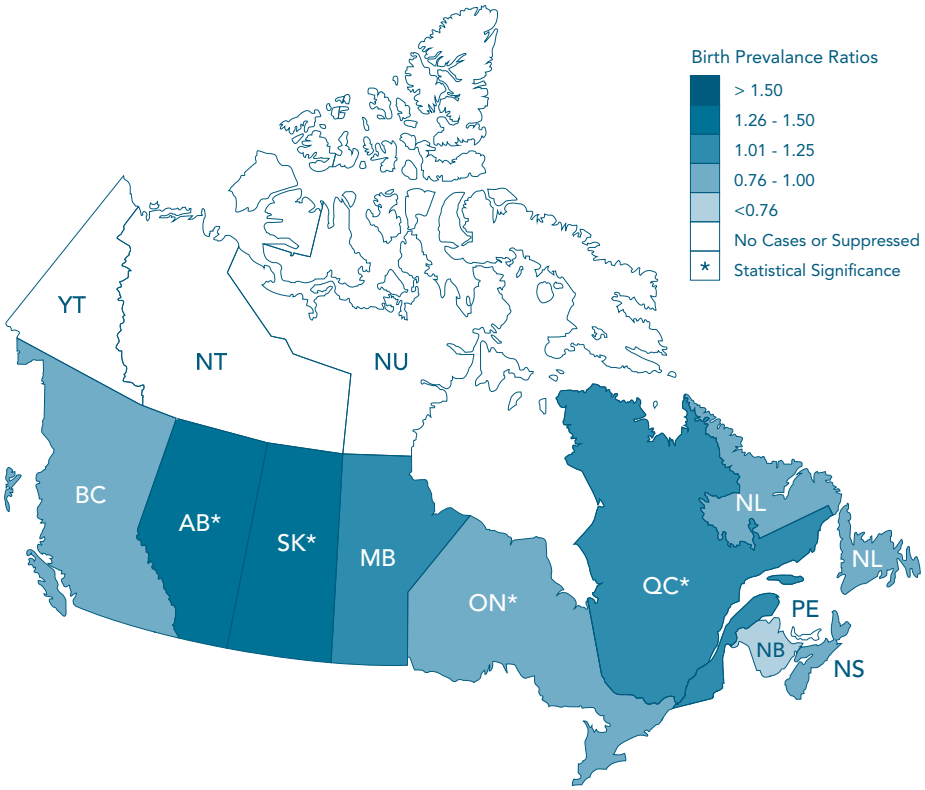
Limb deficiency defect (LDD) rate, by province/territory, *Canada, 1998–2007 combined*



Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1998–2007.
*Total births include live births and stillbirths. §Rate suppressed due to small cell counts (<5). CI—Confidence Interval

FIGURE 6.2B

Ratio of provincial/territorial limb deficiency defect rate to national rate,** *Canada, 1998–2007 combined*



Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1998–2007.
**This ratio calculates the birth prevalence rate per 10,000 total births of each individual province/territory to the birth prevalence rate for Canada during the specified time period. The birth prevalence for Canada includes cases for which province/territory is unknown.

PROVINCIAL AND TERRITORIAL PREVALENCE RATES

Provincial and territorial rates from 1998–2007 are shown in Figure 6.2A. The LDD rate varied among Canadian provinces and territories (Figure 6.2B). This variation may be due in part to differing data sources (CIHI, ACASS, MED-ÉCHO) and coding practices. Uptake of prenatal diagnosis and the likelihood of termination of affected pregnancies are also factors that may influence rate differences. Identification of specific genetic or environmental risk factors that could be contributing to regional variation would require more detailed epidemiological evaluation.

INTERNATIONAL COMPARISONS

The data presented in Table 6.1 are from surveillance programs that, like the Canadian Congenital Anomalies Surveillance System (CCASS), include live births and stillbirths, but not early terminations of pregnancy.[11] Canada's rate is similar to those of Ireland, Slovak Republic, Spain and Japan. Data from Chilean and South American registries indicate the highest rate (9.7 per 10,000 and 9.3 per 10,000 total births, respectively). These increased rates potentially reflect limited access to prenatal diagnosis and termination of pregnancy. In Brazil, for example, where terminations of pregnancy are illegal, the use of misoprostol, an abortifacient, could have increased rates.[15,33] An additional factor potentially contributing to the high rates in Brazil could be the continued use of thalidomide to treat conditions such as leprosy.[34] Diet, nutrition, environmental exposures (e.g., tobacco smoke and other forms of air pollution), altitude and inherent ethnic differences[22] may also contribute to these differences in rates.

TABLE 6.1
Limb deficiency defect (LDD) international rate, by region/country, *2007*

Country/Region	Rate of LDD*
CANADA†	3.5
Japan	3.0
Ukraine	5.1
Slovak Republic	2.8
Spain	4.6
Dublin, Ireland	3.4
Mexico	6.1
Maule, Chile	9.7
South America	9.3

Source: International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) Annual Report, 2009 (data from 2007).
†Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 2007. *Per 10,000 total births.

IMPACT OF PRENATAL DIAGNOSIS ON BIRTH PREVALENCE OF LDD

Major limb defects can be diagnosed prenatally by second trimester ultrasound. Depending upon the type of LDD, the presence of other malformations and ultrasound screening policies, the reported detection rate for isolated LDDs varies from 20%–64%.[35] As noted, prenatal diagnosis potentially influences rates both nationally and internationally.

PREVENTIVE MEASURES

The avoidance of risk factors, such as certain medications and smoking, will help to reduce prevalence of LDDs. The potential protective effect of nutritional factors will require further study.

Ongoing surveillance of LDDs in Canada will be necessary to examine the impact of risk factors and effectiveness of risk reduction strategies.

SUMMARY

LDDs are a complex and highly variable group of congenital limb malformations. The thalidomide tragedy highlighted the importance of birth defects surveillance and more specifically for these defects. Since that time, a variety of environmental risk factors have been proposed to be associated with LDDs. Ongoing surveillance combined with epidemiological analysis is essential in order to establish true prevalence rates and the importance of specific risk factors.

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CHAPTER 7

GASTROSCHISIS

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Erik Skarsgard

INTRODUCTION

Gastroschisis is a defect of the abdominal wall of the developing fetus resulting in extrusion of the intestines into the amniotic space. The defect is typically located to the right of the umbilicus and can usually be detected during pregnancy by a combination of maternal serum screening and ultrasound. Unlike omphalocele, which is frequently associated with other anomalies, gastroschisis is usually an isolated defect. Treatment consists of either urgent surgical closure or delayed closure after gradual reduction of herniated viscera using a preformed silo, which is placed over the bowel and through the defect. Survival in gastroschisis exceeds 90%,[36] however, babies suffer variable degrees of morbidity related to the severity of bowel injury present at birth. A temporal increase in the incidence of gastroschisis has been observed in many countries, including Canada. The reason for this increase is unclear, but is the focus of epidemiologic studies worldwide.

RISK FACTORS

The cause of gastroschisis is unknown, but is presumed to be due to multiple factors. The most widely accepted hypothesis is that of vascular disruption, either of the right umbilical vein[1] or the right vitelline artery,[2] which predisposes to focal weakness and disruption of the paraumbilical abdominal wall. Most cases are sporadic. Although it is generally accepted that additional malformations are uncommon, recent Canadian data suggest that such defects may be responsible for stillbirths and early neonatal deaths that might not otherwise have been attributed to associated anomalies, suggesting a "hidden mortality" due to associated anomalies.[3]

The most consistently observed epidemiologic phenomenon of gastroschisis is the inverse relationship between maternal age and birth prevalence. A population based study of 395 cases from Florida identified an adjusted relative risk (RR) of 3.4 in the under 20 year of age cohort, and of 1.9 in the 20–24 year cohort compared to the reference group of 25–29 years.[4] Aggregate data (936 cases) from EUROCAT reported an RR of 7.0 in the under 20 year, and of 2.4 in the 20–24 year group compared to the 25–29 year reference group.[5] This phenomenon has been consistently observed in the majority of studies.[6-8] It is not clear whether the observed temporal increase is due exclusively to increased prevalence within the teenage mother population,[9] or whether the overall prevalence increase is attributable to increased prevalence at birth in all age groups.[10,11]

Studies of risk related to paternal age (adjusted for young maternal age), suggests that young paternal age may be an independent risk factor. One study reports a 1.6 fold increase in risk per 10 year reduction in paternal age,[11] while a second suggests a 1.5 fold increased risk of affected offspring in a 20–24 year group compared to the 25–29 year group.[12]

Among teenage mothers and those aged 20–24 years, whites appear to be at increased risk compared with blacks and "other" ethnicities.[13] However, in another study in which ethnicity categories were adjusted for maternal age, mothers of Hispanic ethnicity were more likely to have an affected infant than those who were white.[14]

Measures of socioeconomic status (SES) have also been examined. In an analysis controlled for maternal age, an annual family income of less than $10,000 was associated with an increased likelihood of gastroschisis compared to a referent family income of $50,000 or more (RR=4.5).[7] However, other factors frequently reflective of SES, such as maternal education level, have not been found to confer increased risk.[7,15]

The association between cigarette smoking and gastroschisis has been widely studied, with most studies suggesting a moderate risk increase among mothers who smoke during pregnancy, with RR adjusted for maternal age ranging from 1.5–2.0.[16-18] One study suggested a dose-response relationship with higher rates among mothers who smoked 20 or more cigarettes per day.[19] Studies of maternal alcohol consumption have shown a relationship between first trimester alcohol consumption (including binge drinking) and the risk for gastroschisis, with an observed two to three fold increase in incidence.[7,15] Maternal exposure to illicit drugs is another postulated risk factor, with most studies relying on self-reporting as the method by which exposure is documented. Among drugs evaluated in age-matched controlled studies, the strongest associations emerge with cocaine: odds ratio (OR)=1.7–4.6, marijuana (OR=3.0) and methamphetamines (OR=0.9–1.8).[7,18,19] In addition to increasing risk of gastroschisis, non-therapeutic exposures are also associated with poorer functional outcomes, as well as more severe bowel injury noted at birth. In one Canadian study, infants of mothers who had smoked took significantly more days to recover before they were able to tolerate enteral nutrition[20] and, in a second study, cocaine use was associated with a higher severity of bowel injury (e.g., perforation, necrosis or atresia) detected at birth.[21] A study from Washington State has shown an association with month of birth that persisted on multivariate analysis, suggesting that infants born in January, February or March are twice as likely to have gastroschisis as infants born in other months.[22] This finding raises the possibility that infection might be playing a role in causation. Another study supportive of an infectious contribution suggests that gastroschisis is more common in infants of women who had a genitourinary infection in the month preceding pregnancy or during the first trimester. Women who reported both a urinary tract infection and a sexually transmitted disease had a significantly increased risk.[23] Environmental exposure data from the Washington State study linked maternal residence distance to high surface water herbicide (e.g., atrazine) concentrations to an increased risk.[24] In this same study, spring conception (coinciding with herbicide spraying) was also associated with a higher birth prevalence, raising the concern that controllable environmental exposures may contribute to risk.

Recent data suggest a relationship with pre-pregnancy body mass index (BMI). One study observed a higher rate in underweight compared to normal weight mothers, with an OR adjusted for age and ethnicity of 3.0.[25] Two other studies have demonstrated a lower risk in mothers who are overweight or obese, compared to those of normal weight.[26,27]

Dietary markers of good and poor nutrition were correlated with gastroschisis occurrence in an age-matched case control study.[28] Dietary intake data for the three months preceding conception were recorded and diets were classified as either low or adequate for a-carotene and glutathione (both anti-oxidants), and normal or high nitrosamine. This study identified associations on multivariate analysis between low a-carotene, low total glutathione and high nitrosamines and gastroschisis. Another dietary study considered the relationship with dietary fats, based on a hypothesized relationship between dietary fat and vasoconstriction leading to fetal vascular disruption.[29] This case-control study looked at dietary fat intake in the year prior to conception and found that there was an association, albeit weak, between total fat intake in the middle and high centiles and the occurrence of gastroschisis.

A number of studies have looked at the effect of prenatal exposure to therapeutic medications. Evidence supporting increased risks among women using aspirin, ibuprofen or acetaminophen is weak overall, but strongest for aspirin with OR on multivariate analysis ranging from 2.7–20.4.[18,30] Studies looking at maternal decongestant use are inconsistently associated with increased risk.[15,31]

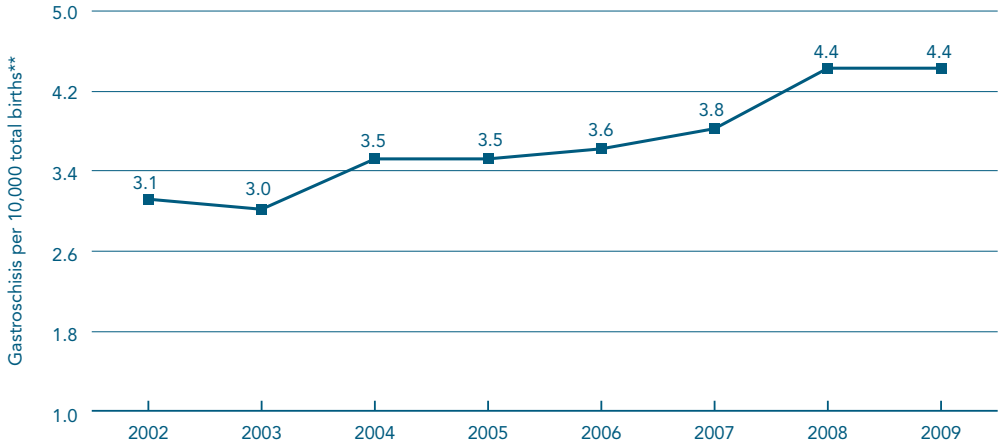
PREVALENCE RATE OF GASTROSCHISIS IN CANADA

Based on aggregate data from 2002 to 2009 from the Canadian Congenital Anomalies Surveillance System (CCASS), the prevalence rate of gastroschisis in Canada is 3.7 per 10,000 total births. Over this time period there has been a gradual increase in prevalence (Figure 7.1), similar to reports from many other countries. Specifically, the rate of gastroschisis in Canada (excluding the province of Québec) increased from 3.1 per 10,000 total births (i.e., live births and stillbirths) in 2002 to 4.4 per 10,000 total births in 2009, which corresponded to 129 individual cases for 2009. This represents an increase of 43.8% (P=0.015). The reason for this rise in prevalence is unknown.

The rates presented in this report were restricted to 2002–2009 because prior to 2002 CCASS used the International Classification of Diseases (ICD)-9 codes where gastroschisis and omphalocele (and prune belly syndrome) could not be differentiated, as they were all under one code (756.7). ICD-10 gave them separate codes. The province of Alberta used the British Pediatric Association expansion of the ICD-9, which did differentiate them.

FIGURE 7.1

Gastroschisis rate, *Canada, 2002–2009**



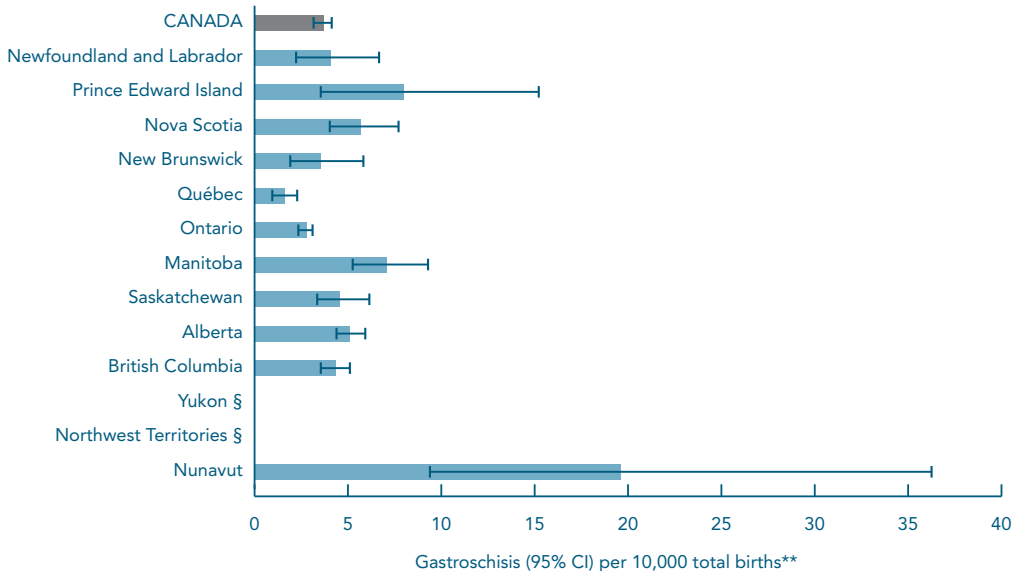
Source: Public Health Agency of Canada, Canadian Congenital Anomalies Surveillance System, 2002–2009.
*Some provincial data were only available for certain years: New Brunswick (2004–2009), Québec (2006–2007) and Manitoba (2005–2009). All others were available for the full period (2002–2009). **Total births include live births and stillbirths.

PROVINCIAL AND TERRITORIAL PREVALENCE RATES

The birth prevalence of gastroschisis varies considerably across Canada (Figures 7.2A and B). In 2002–2009, the rates ranged from 19.6 (95% CI 9.4–36.1) per 10,000 total births in Nunavut to 1.6 (95% CI 1.1–2.4) in Québec. Although small changes in case numbers could markedly influence rates in areas with few births, maternal age differences may explain some of this difference as the age specific fertility rate for 10–19 year olds in 2004 was 59.2 (95% CI 51.1–68.1) per 1,000 females in Nunavut compared to 5.1 (95% CI 4.9–5.3) per 1,000 females in Québec.[32] Rates of smoking in pregnancy also show geographic differences with Nunavut again having very high rates.[32]

FIGURE 7.2A

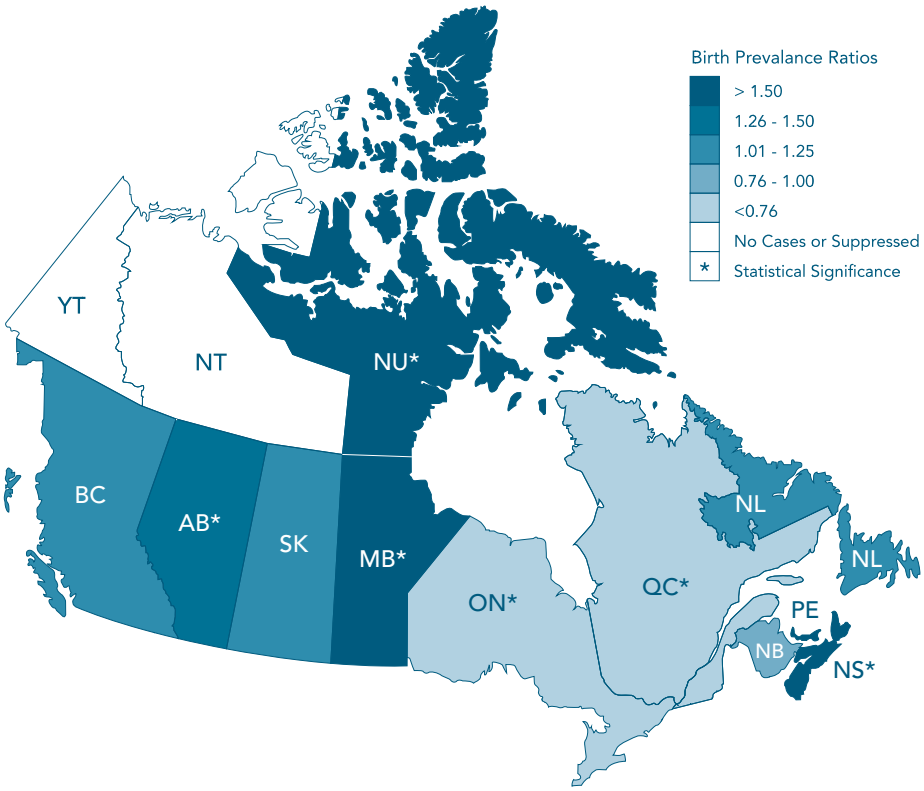
Gastroschisis rate, by province/territory, *Canada, 2002–2009* combined*



Source: Public Health Agency of Canada, Canadian Congenital Anomalies Surveillance System, 2002-2009.
*New Brunswick 2004-2009, Manitoba 2005-2009 and Québec 2006-2007. **Total births include live births and stillbirths.
§ Rate suppressed due to small cell numbers (<5). CI—Confidence Interval

FIGURE 7.2B

Ratio of provincial/territorial gastroschisis rate to national rate,** *Canada, 2000–2009 combined*



Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 2000–2009.
**This ratio calculates the birth prevalence rate per 10,000 total births of each individual province/territory to the birth prevalence rate for Canada combined for the eight-year period 2002–2009, with the exception of New Brunswick 2004–2009, Manitoba 2005–2009 and Québec 2006–2007. The birth prevalence for Canada includes cases for which province/territory is unknown.

INTERNATIONAL COMPARISONS

Table 7.1 illustrates the variation in prevalence of gastroschisis worldwide. Prevalence rates for 2007 range from a low of 0.7 cases per 10,000 births in Campania-Italy to a high of 9.4 cases per 10,000 births in South America. Geographical differences in prevalence have also been reported within Europe by EUROCAT, with higher rates of gastroschisis in the United Kingdom and lower rates in more southerly countries such as Italy, even after adjusting for maternal age.[10] In the United States, the state of Texas reported a 5.1% annual increase in prevalence during 1999–2007[33] and North Carolina reported a 130% increase from 1997 to 2000, a shift from 2.0 to 4.5 per 10,000 live births, primarily due to lower maternal age.[34] Similar to the Canadian data, most registries reporting to the International Clearinghouse for Birth Defects Surveillance and Research showed higher prevalence rates in 2007 compared to previous periods.[35]

IMPACT OF PRENATAL DIAGNOSIS ON BIRTH PREVALENCE OF GASTROSCHISIS

Most cases of gastroschisis are now diagnosed antenatally; the British Isles Network of Congenital Anomaly Registrars registry for the United Kingdom showed 97% of cases being diagnosed antenatally,[36] while Canadian figures showed that 94% were diagnosed antenatally.[37] Less than 10% of cases are associated with other congenital anomalies and terminations for isolated defects are infrequent. Hence, prenatal diagnosis appears to have had little impact on the prevalence at birth of gastroschisis.

TABLE 7.1
Gastroschisis international rate, by region/country, *2007*

Country/ Registry	Rate of gastroschisis*
CANADA†	3.8
Alberta, Canada	4.9
British Columbia, Canada	5.0
Victoria, Australia	1.9
Western, Australia	3.7
Chile	2.2
Finland	3.7
Campania, Italy	0.7
Japan	1.9
South America	9.4
Sweden	1.7
Wessex, United Kingdom	4.8
Wales, United Kingdom	3.8
Atlanta, USA	5.9
Texas, USA **	5.1
Utah, USA	5.1

Source: International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) Annual Report, 2009 (data from 2007)
*Per 10,000 total births. **Source: Texas, 2006 data.
†Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 2007.

PREVENTIVE MEASURES

The strong association with young maternal age[4-11] and also the observed relationship with maternal undernutrition[25,28] indicate that reduction in teenage pregnancy rates and ensuring good maternal nutrition may help reduce risk, as would avoidance of maternal smoking, alcohol use and other high risk behaviours. Ongoing epidemiological studies may identify other modifiable risk factors.

SUMMARY

Gastroschisis is one of the more serious congenital anomalies, requiring urgent surgical and medical intervention at birth. The mortality rate is approximately 5%[37] and morbidity with prolonged hospital stay and occasionally intestinal failure is significant.[37,38] It is vital that continued surveillance efforts are directed towards monitoring the increasing prevalence in Canada and its regional variability, as well as identifying the factors—environmental, pharmacological or otherwise—that may be contributing to this increase.

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CHAPTER 8

PRIMARY PREVENTION: MODIFIABLE RISK FACTORS

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Prevention involves avoidance of disease through deliberate strategies that take into consideration knowledge of risk factors and their pathophysiologic influences. Avoiding fetal/neonatal disease is likely to be cost effective given the emotional, economic and health services resources needed to deal with lifelong morbidity. The *in utero* environment is influenced by maternal exposures such as medication use, lifestyle and environmental risk factors, all of which are also influenced by socioeconomic status (SES). Nutrition also influences fetal development. Correcting nutrient deficiencies is important with the caveat that over-correction may have its own inherent risks. In addition, maternal demographics are changing and these changes also have the potential to alter fetal outcome. Genetic risk from advanced and very young maternal age or chronic maternal medical conditions can negatively impact fetal/neonatal outcomes.

Primary prevention issues for congenital anomalies have been arbitrarily categorized into: (1) maternal environmental/SES factors; (2) nutritional factors; and (3) the influences of maternal age along with common chronic medical diseases.

MATERNAL ENVIRONMENT AND SOCIOECONOMIC FACTORS

SES is closely related to health outcomes, including perinatal and infant health. SES is measured using a combination of indicators such as education, occupation and individual/family income since these factors are often closely interrelated.[1] Low social status is a well-established risk indicator for adverse perinatal and infant outcomes such as low birth weight, preterm birth, stillbirth and perinatal, neonatal or post neonatal mortality.[2] More socioeconomically deprived groups have higher non-chromosomal congenital anomaly rates, part of which may be explained by differences in nutritional status. Higher risks of neural tube defects (including spina bifida and anencephaly) have been reported in populations with lower SES.[3] Trends towards higher risks in lower social classes have also been reported for orofacial clefts[4] and possibly for selected congenital heart defects.[3] Among residents of more socioeconomically deprived areas, both higher and lower birth prevalence rates of Down syndrome have been reported.[5] Average age at first delivery usually increases with social status thus, in Down syndrome and similar trisomies that are associated with higher maternal age, there is a greater risk with higher social status. It is important to note that while SES inequalities in rates of anomalies *in utero* differ with type of anomaly, there are also socioeconomic variations in access to prenatal diagnosis and screening and in termination of pregnancy rates. This can lead to a widening of SES inequalities in the rate of live births and neonatal deaths associated with both chromosomal and non-chromosomal anomalies.[2]

Several studies suggest that maternal smoking during pregnancy is associated with an increased risk of defects of the cardiovascular, orofacial clefts, musculoskeletal and gastrointestinal systems.[6] These specific defects should be included in public health educational information to encourage more women to stop smoking before or in early

pregnancy; in particular, younger women and those from lower socioeconomic groups, in which smoking prevalence is greatest, should be targeted.

Alcohol exposure during pregnancy can have many adverse effects on the developing fetus, resulting in a spectrum of birth defects that can negatively affect a child's growth, cognition, physical appearance and behaviour. This spectrum of disorders is referred to as fetal alcohol spectrum disorders (FASD). Fetal alcohol syndrome (FAS) is the most serious disorder within this spectrum and is one of the leading causes of preventable birth defects and mental handicap. Several maternal risk factors, including advanced maternal age, illicit drug use, history of previous pregnancy with FASD, lower SES and malnutrition in combination with fetal exposure to alcohol are associated with a higher risk of FASD.[7,8]

The use of medications during pregnancy poses a potential risk to both the mother and fetus. The effect of many medications on the outcome of pregnancy are unknown, therefore the safest pregnancy-related option is to take as few medications as possible. However, almost every pregnant woman is exposed to some type of medication during pregnancy.[9] Women with a history of psychiatric, seizure-related or hematologic illnesses frequently require medication throughout pregnancy. In such patients, care must be taken to select the safest drug from the relevant class of medication. An estimated less than 1% of birth defects may be caused by pharmaceutical drugs.[10] Among the commonly used over-the-counter medications, acetaminophen, chlorpheniramine, kaolin and pectin preparations, and most antacids have a good safety record. With all medications used during pregnancy, the benefit of the drug should outweigh the risk to the fetus, being that less than 1% of pharmaceuticals are considered to pose no human teratogenic risk.[9]

According to the Public Health Agency of Canada's Maternity Experiences Survey, 7% of Canadian women reported having used recreational drugs in the three months prior to pregnancy and 1% reported recreational drug use during pregnancy. Women living in low-income households and younger mothers were more likely to report having used illicit drugs both prior to and during pregnancy.[11] Recreational drug use during pregnancy is associated with low birth weight, preterm birth, developmental and behavioural issues during childhood, gastroschisis and neuroblastoma.[11–13]

Environmental risk factors such as residence near industrial sites or socioeconomically deprived areas have also been studied in association with congenital anomalies. Increases in risk of adverse health effects (low birth weight, birth defects and certain types of cancers) have been reported near individual landfill sites. Typically, people of lower SES are more highly exposed to pollution, either because housing prices are lowest near landfills and other potentially hazardous locations, have less power or advocacy skills to prevent exposure, have less access to environmental health information, or because aspects of lifestyle associated with greater deprivation (such as inability to buy bottled water) lead to higher exposure.[14]

Embryonic and fetal infections, including cytomegalovirus, varicella, rubella and toxoplasmosis infections are also considered causes/suspected causes for certain congenital anomalies.[15] Vaccination for rubella is an example of successful primary prevention of congenital anomalies due to a known viral teratogen. Cytomegalovirus and toxoplasmosis are now the most common known infectious teratogens. Research is needed to determine population incidence and options for screening/diagnosis, as well as treatment for these potential fetal threats.

NUTRITION

Good nutrition is critical for appropriate fetal development and an overall healthy pregnancy. A number of specific nutrients have been thought to be associated with risk for congenital anomalies. The best studied example is folic acid, for which suboptimal status is associated with increased risk for neural tube defects (NTDs). Two key randomized clinical trials in the 1990's clearly demonstrated that folic acid supplementation in the periconceptional period prevented the primary occurrence and

secondary recurrence of NTDs by approximately 70%.[16,17] As such, it is recommended that women of childbearing age who could become pregnant take a daily multivitamin supplement containing 0.4 mg (400 µg) folic acid.[18] In addition, since November 1998, the Government of Canada has mandated folic acid fortification of white flour, pasta and some other cereal-based products to increase folic acid intake by approximately 150 µg per day among women of childbearing age. As a result, the incidence of NTDs in Canada has declined by approximately 45%.[19]

While the weight of evidence for other nutrients does not equate to that for folic acid and NTDs, observational and case-control studies have indicated that achieving an adequate intake of many nutrients could prevent a number of anomalies (Table 8.1). The associations reported between specific nutrients and various congenital anomalies are not always consistent. However, the use of multivitamin supplements during pregnancy is associated with reduced risk for a number of congenital anomalies such as those noted in Table 8.1.[20] Also, deficiency for many nutrients has been associated with pregnancy complications, such as preterm delivery, pregnancy-associated anemia, small-for-gestational-age and preeclampsia. The evidence therefore emphasises the need for women to achieve adequate intakes of all nutrients through a well-balanced diet and a multivitamin supplement for a healthy pregnancy.[18,21] For folic acid in particular, the Public Health Agency of Canada recommends that supplements be started prior to pregnancy.

Women should be cautioned against over-consuming supplemental vitamin A as it has teratogenic effects and is associated with increased risk for limb and heart defects.[38,39]

TABLE 8.1

Low nutrient intake/status as potential risk factors for congenital anomalies

Congenital anomaly	Nutrient(s)
Neural tube defects[22–24]	Folate/folic acid, vitamin B12, vitamin B6, riboflavin, choline, vitamin C, vitamin E, vitamin A, beta-carotene, iron, niacin, magnesium and lutein
Congenital heart defects[25–27]	Folate/folic acid, vitamin B12, riboflavin and nicotinamide
Cleft lip with or without palate[28–31]	Folate/folic acid, thiamine, niacin, vitamin A, vitamin C, iron, vitamin E, magnesium and vitamin B6
Limb deficiencies[32]	Folate/folic acid, vitamin B6 and riboflavin intakes
Hypospadias[33]	Choline, methionine and vitamin B12
Congenital diaphragmatic hernia[34]	Folate/folic acid, choline, thiamine, riboflavin, vitamin B6, vitamin B12, calcium, iron, magnesium, zinc and vitamin E
Fetal bone mineral accrual and bone morphology[35]	Vitamin D
Eye development[36]	Vitamin A
Neurodevelopment and cognitive development[37]	Omega-3 fatty acids

MATERNAL CHRONIC DISEASE

Many maternal chronic diseases are associated with an increased risk of fetal congenital anomalies or post-natal developmental abnormalities. For some pregnant women, a number of these medical conditions may co-exist and all increase in prevalence with advanced maternal age. Age demographics for pregnant women continue to change with increasing numbers of women choosing to delay childbearing. Age-specific fertility statistics show that, for women aged 40–44 years, the fertility rate has more than doubled between 1986 and 2008 (from 3.4 to 8.4 per 1,000 births).[40] The percentage of pregnant women over the age of 35 years also continues to increase, from 13.4% in 1996 to 18.1% in 2008.[41,42] In addition to the known genetic risks for the fetus, these older mothers are at higher risk of having or developing chronic medical conditions that can impact fetal and newborn health. Some common maternal medical conditions that are known to influence fetal outcome are obesity, hypertension, diabetes and thyroid disease. Older women also tend to have older partners and there are independent factors associated with late paternal age, especially increased risks for *de novo* genetic mutations.

Maternal obesity has been associated with an increased risk of many congenital anomalies, including neural tube defects, congenital heart defects, orofacial clefts, hydrocephalus, anorectal atresia and limb reduction abnormalities.[43,44] There appears to be a relationship to severity of obesity.[45] Although it is accepted that obesity likely is an independent risk factor for congenital anomalies, other co-existing factors such as diabetes may account for some of the increased risk. In addition, antenatal congenital anomaly detection rates are lower in obese women, leading to an increased rate for neonatal congenital anomalies.[46] The rate of maternal obesity has increased dramatically. In North America, the rate of obesity among 20 to 39-year-old females has gone from 9.3% in 1986–92 to 20.9% in 2007–2008.[47] Maternal obesity can also develop in pregnancy, particularly among women of low SES. According to the 2006 Maternity Experiences Survey, women who are young, primiparous, less educated or Aboriginal tend to gain more weight than is recommended during pregnancy.[48] This, in turn, has been shown to be associated with postpartum weight retention and places these individuals at higher risk in subsequent pregnancies.[48]

The prevalence of diabetes is increasing and this is likely related to sedentary lifestyle and obesity. Between 2000 and 2010, the prevalence of diabetes in the entire Canadian population has increased 103% and is currently at 7.6%. Pre-diabetes within the population is 21.8%.[49] Diabetes in pregnancy has also increased. Pre-gestational diabetes has more than doubled between 1999 and 2005 (0.8% to 1.8%) as shown in a study in USA.[50]. In 2008/09, close to 2.4 million Canadians aged one year and older were living with diagnosed diabetes (either type 1 or type 2), which represented approximately 6.8% of the population.[51] There is a direct relationship between age and incidence of diabetes. For all men and women aged 18–34 years, it was 0.9%; for those aged 35–44 years, it was 2%.[52] With pre-gestational diabetes, the risk of both spontaneous abortion and congenital anomalies is increased. The risks are directly related to glycemic control in early pregnancy (less than nine weeks menstrual dating). Among these women, the overall risk for congenital anomalies is approximately 6%, which is double that in the non-diabetic population.[53] Other fetal effects include fetal growth abnormalities. Accelerated fetal growth can be initiated by poor early glycemic control. Larger infants are at increased risk for birth injury and hypoxia due to shoulder dystocia. Postnatally, they are at higher risk to develop obesity, diabetes and attention disorder.[54] Maternal diabetes, particularly with vascular complications, can also be associated with fetal growth restriction. These infants are at higher risk for neurodevelopmental delay.[55]

Maternal thyroid disease and thyroid medication use have been linked to selected birth defects such as congenital heart disease, hydrocephaly,

hypospadias and isolated anorectal atresia.[56] In addition, both hypo- and hyperthyroidism are associated with other adverse perinatal outcomes. Hyperthyroidism is linked to low birth weight and pre-term birth and, on rare occasions, to fetal/neonatal goitre.[57,58] Neonatal hypothyroidism results in severe mental handicap, but overt maternal hypothyroidism is also associated with postnatal neuropsychological and cognitive impairment. There is also an increased risk for postnatal neurocognitive dysfunction with maternal subclinical hypothyroidism, but it is unclear whether this is an independent risk factor or due to the increased rate of preterm birth with this condition. The risk of thyroid disease in pregnancy is related to age, obesity and family history. Approximately 1% of pregnant women have overt thyroid dysfunction; 2–3% have subclinical hypothyroidism and 10–15% are antibody positive.[59]

SUMMARY

Primary prevention avoids the suffering and cost associated with congenital anomalies. This chapter has outlined many factors that increase congenital anomaly occurrence, but are amenable to prevention strategies. There have been prior successes such as the fetal benefits of adequate nutrient intakes—particularly dramatic with folic acid food fortification. SES, many environmental factors, obesity and chronic diseases are recognized as having widespread importance for public health, in addition to specifically consequences for the developing fetus. Nutritional factors require public education, ready access to good nutrition for expectant mothers, as well as research on the need for proper nutrient supplements or additives. Finally, the public requires ongoing education on the risks inherent with the age extremes of reproductive potential.

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CHAPTER 9

SECONDARY PREVENTION: PRENATAL SCREENING AND DIAGNOSIS

R. Douglas Wilson

INTRODUCTION

Primary prevention is a strategy designed to avoid the initial occurrence of a disease or condition. Secondary preventive measures are used for the early identification, treatment and/or management of an existing disorder for the purpose of reducing or preventing morbidity. The distinction between primary and secondary prevention as it relates to congenital anomalies (CAs) is less clear. Prenatal diagnosis and, in some cases, subsequent termination of pregnancies with a CA is considered one method of secondary prevention in that it reduces birth prevalence, but other strategies can be used to ameliorate the impact of existing disease. These include prenatal detection, ultrasound monitoring and early intervention to reduce associated co-morbidities either before birth or soon after. A multidisciplinary maternal, fetal and neonatology team approach to determining the most effective time, place and means of delivery of an affected infant supports early intervention and treatment. Genetic counselling (including provision of recurrence risks and methods to reduce them) of the parents and other individuals at risk can also be an effective means of secondary prevention.

This review is focussed on the six types of anomalies highlighted in this report: Down syndrome, neural tube defects, congenital heart defects, orofacial clefts, limb deficiency defects and gastroschisis. Prenatal screening and diagnosis take different approaches based on the congenital anomaly. The previous *Congenital Anomalies Report*[1] provided a basic summary for prenatal screening and testing. Over the last decade, there have been major screening and diagnostic advances beyond fetal aneuploidy and neural tube defects. Major fetal CAs, identified during pregnancy, are estimated to be 1–3%.[2] Follow up in the neonatal population usually increases the congenital anomaly incidence (see Chapter 1 on overall prevalence) and emphasizes that only some structural defects (e.g., malformation, deformation, disruptive categories) are identified prenatally by the screening imaging techniques.

SCREENING/DIAGNOSTIC TECHNIQUES

Fetal CA screening uses the systematic application of a test (e.g., ultrasound, maternal serum analytes) in order to identify fetuses at sufficient risk of a specific disorder to warrant further investigation such as amniocentesis. These screening tests usually involve fetal surveillance in the first and/or second trimester by ultrasound and maternal serum screening (e.g., biochemical analytes, quantitative protein levels, fetal molecular sequences). The biological effects and safety of obstetrical ultrasound have been reviewed by Bly et al.[3]

Prenatal diagnosis usually involves an invasive diagnostic test using fetal-related tissues such as placental specimen by chorionic villus, fetal cells by amniocentesis, fetal blood cells or serum by cordocentesis or direct fetal biopsy of skin or muscle. Diagnostic fetoscopy has been used on a limited basis due to improving imaging technology, which has rendered fetoscopy less warranted. These invasive procedures have an increased risk of fetal loss or damage above the background risk when no procedure is undertaken.

Additional imaging such as Magnetic Resonance Imaging (MRI) (e.g., central nervous system, lungs, heart, abdomen/renal, limbs)[4–6] or low radiation computed tomography (CT) scan (e.g., skeletal dysplasia/anomalies)[7–10] usually functions as second tier screening, assisting in triaging, or directing the

differential diagnosis for invasive testing, after which molecular diagnostic testing can be confirmatory. At times, such imaging can be diagnostic if pathognomonic features are present.

If a pregnancy with an anomaly is terminated or ends spontaneously an autopsy is recommended, especially when there is no definite diagnosis as this allows for more accurate parental counselling and estimation of recurrence risk. If there is an increased risk of recurrence for the CA, planning for prenatal diagnosis in a subsequent pregnancy and/or other family studies can be considered.

Though not without significant ethical, legal and practical implications,[11] it is now feasible to sequence the fetal genome from maternal blood. For Down syndrome, it is likely that deoxyribonucleic acid (DNA) sequencing of maternal plasma (combined DNA 90% maternal and 10% fetal) will remain as a screening test, possibly as a second tier screen prior to invasive prenatal testing, until large scale clinical testing provides accurate data on true sensitivity, specificity and cost within prenatal assessment.[12] In a cohort of 4,664 "high risk" women, who were also undergoing invasive diagnostic testing by traditional biochemical analyte and ultrasound screening criteria, the reported trisomy 21 detection rate using maternal serum was 98.6%, the false positive rate was 0.2% and the test failed in 0.8%.[12] Similar detection rates based on maternal serum screening were seen for trisomies 13 and 18 in a later study of the same sample cohort.[13]

Table 9.1 summarizes screening and diagnostic factors used in prenatal testing, during each trimester, while Table 9.2 summarizes characteristics of ultrasound-guided diagnostic procedures and their associated risks and accuracy.

TABLE 9.1

Summary of screening and diagnostic factors used in prenatal testing, by trimester

Screening/Diagnostic Factor	1st Trimester	2nd Trimester	3rd Trimester
Timing of ultrasound screening [4,33-39]	increasing opportunity	standard of care	fetal growth, AF volume, physiology
Timing of diagnostic procedure (singleton, twins)[19,32]	CVS	CVS amniocentesis cordocentesis	CVS amniocentesis cordocentesis
Neural tube defect diagnosis[5,6,11]	ultrasound opportunity	ultrasound 100% MSAFP 95%	–
Molecular trisomy screening[12,13]	MS at >7 weeks	–	–
Other imaging techniques[5,7-10,40]	–	MRI >20 wks low dose CT >18 wks	–

AF—amniotic fluid, CVS — chorionic villus sampling (placental biopsy), MSAFP—maternal serum alpha fetoprotein, MS—maternal serum, MRI—magnetic resonance imaging, CT—computer tomography

TABLE 9.2

Summary of ultrasound-guided diagnostic procedures, associated risks and accuracy

	CVS	Amniocentesis	Cordocentesis
Fetal tissue to be analyzed[41,42]	placenta	amniotic fluid	blood
Timing of procedure[41,42]	1st, 2nd,3rd trimester	2nd, 3rd trimester	2nd, 3rd trimester
Testing results[41,42]	chromosomes molecular	chromosomes molecular	chromosomes molecular
Pregnancy loss risk in addition to background loss rate[41,42]	TA 1–2% TC 2–6%	TA 0.5–1.0%	TA 2–3%
Testing accuracy	accurate with 1–2% CPM	accurate	accurate

CVS—chorionic villus sampling, TA—transabdominal approach, TC—transcervical approach, CPM—confined placental mosaicism

FETAL THERAPY

A review of fetal therapy indication, techniques and outcomes has been recently published.[14] The option of fetal therapy could increase the prevalence among live births of certain congenital anomalies such as myelomeningocele, diaphragmatic hernia, pulmonary anomalies (e.g., congenital cystic adenomatoid malformation, bronchopulmonary sequestration, pleural effusion), and urinary tract obstructive anomalies.

IMPACT OF PRENATAL TESTING

Previous publications have looked at the impact of prenatal screening and diagnosis on the epidemiology of structural congenital anomalies. Chi et al.[15] reported on abdominal wall defects, renal agenesis/dysgenesis, and limb reduction defects. They found that marked increases in prenatal diagnosis occurred over the study period, but not in the proportions of pregnancies terminated, concluding that for these CAs, prenatal testing had made little impact on their prevalence.

More recent monitoring of prenatal detection of structural fetal congenital anomalies in England and Wales identified 2,883 births with congenital anomalies from a cohort of 601,545 live births and stillbirths.[16] The congenital anomalies evaluated included anencephaly, spina bifida, serious cardiac anomalies, diaphragmatic hernia, gastroschisis, omphalocele, bilateral renal agenesis, severe/lethal skeletal dysplasia and cleft lip with or without cleft palate. The most frequently reported CAs were serious cardiac defects (14.1 per 10,000 total births) and cleft lip with or without palate (9.7 per 10,000 total births). The least reported anomalies were bilateral renal agenesis and lethal/severe skeletal dysplasia at <1.5 per 10,000 total births. Prenatal diagnosis varied from 53.1% for serious cardiac anomalies to 99.6% for anencephaly. The least variation in prenatal diagnosis rates was seen for anencephaly and gastroschisis and the greatest for serious cardiac defects and lethal/severe skeletal dysplasia.

PRENATAL DIAGNOSIS REVIEW

DOWN SYNDROME: PRESENT SCREENING PERFORMANCE AND ASSESSMENT

The present performance of aneuploidy screening for trisomy 21 has a detection rate of 90–95% with a false positive/screen positive rate of 2–5%.[17] Chitayat et al.[18] reviewed currently available screening options and their performance. Timing accuracy of prenatal screening options and approaches are provided in Table 9.3. These include maternal serum and first trimester ultrasound aneuploidy screening. Ultrasound second trimester markers (most common) for the detection of fetal trisomy 21[19] include cardiac—structural defects, extra cardiac focus; central nervous system (CNS)—cerebral ventriculomegaly; gastrointestinal—duodenal atresia after 22 weeks gestation, hyperechogenic bowel; fetal non-immune hydrops; thickened nuchal (neck) fold; skeletal—absent/short nasal bone, short femur/humerus and renal—pyelectasis.

TABLE 9.3

Summary of prenatal screening options[19]

	Trimester	Detection rate (DR) %	False positive rate (FPR) %	Odds of being affected for positive result (OAPR)
FTS (MA, hCG, PAPPA, NT)	1st	83	5.0	1:27
Quad (MA, AFP, hCG, Inhibin A)	2nd	77	5.2	1:50
IPS (MA, PAPPA, AFP, hCG, uE3, Inhibin A, NT)	1st/ 2nd	87	1.9	1:10
IPS minus Inhibin A	1st / 2nd	88	3.0	1:20
IPS minus NT (serum only)	1st / 2nd	85	4.4	1:26

FTS— first trimester screening, MA— maternal age, NT— nuchal translucency, AFP—alpha-fetoprotein, hCG— human chorionic gonadotropin, PAPPA— pregnancy associated plasma protein A, uE3— unconjugated estriol 3, DR— detection rate, FPR— false positive rate, OAPR— odds of being affected for a screen positive result, IPS— Integrated Prenatal Screen

NEURAL TUBE DEFECTS: PRESENT SCREENING PERFORMANCE[5]

Screening for neural tube defects (NTDs) includes ultrasound and maternal serum screening with alpha feto-protein (MSAFP). Ultrasound will identify almost all cases of anencephaly and cranial anomalies.[5,6,20] Careful assessment using the posterior fossa Arnold-Chiari malformation in association with imaging of the spine to identify the level of the myelomeningocele defect allows 95% identification of spina bifida.

MSAFP screening for NTDs started in the 1970s with the first population-based screening beginning in Canada in 1985. MSAFP multiples of the gestational age-specific median (MOM) at 16 weeks of gestation are 3.8 MOM and 6.5 MOM for open spina bifida and anencephaly respectively. The typical screen positive cut-off for NTDs screening is 2.0–2.5 MOM. The detection rate using 2.0 MOM is 90%.[20] Positive screens identify women who can be offered fetal assessment with ultrasound, followed by amniocentesis and measurement of amniotic fluid AFP and acetylcholinesterase in equivocal cases. Increased MSAFP values are seen in many other situations such as multiple pregnancy, fetal death, oligohydramnios, placental anomalies, intrauterine growth restriction and pre-eclampsia as well as with other CA including gastroschisis and omphalocele.[20] MSAFP remains a useful screening tool for NTDs and abdominal wall defects, including gastroschisis, especially in those jurisdictions where timely examination by skilled ultrasonographers is not available for all women or if fetal imaging is difficult because of maternal obesity.

CONGENITAL HEART DISEASE: PRESENT SCREENING PERFORMANCE

The American Institute for Ultrasound in Medicine (AIUM) Practice Guideline for the Performance of Fetal Echocardiography was published in January 2011.[21] Maternal indications included autoimmune antibodies, familial inherited disorders, a first degree relative with congenital heart defect (CHDs), in vitro fertilization, metabolic disease and teratogen exposure with cardiac implications. Fetal indications were abnormal cardiac screen, abnormal heart rate/rhythm, fetal chromosomal anomaly, extracardiac anomaly, hydrops, increased nuchal translucency, monochorionic twins and unexplained severe polyhydramnios. Further reviews document the historical and clinical role of fetal echocardiography (ECG),[22] fetal ECG at 11–13 weeks by transabdominal high frequency ultrasound,[23] and an audit of 10 years of referrals for fetal ECG.[24]

Experts in fetal cardiology viewing videoclips of fetal cardiac assessments at 11–13 weeks in 886 fetuses suspected a cardiac anomaly in 100. The obstetricians performing the initial scans detected 95% of these, with a correct diagnosis in 84% as confirmed by the "gold standard" of fetal ECG at 18–22 weeks. The defect was classified as major in 54 cases and minor in 46. A normal cardiac scan was identified in 767 (86.6%) cases and inadequate cardiac views were seen in 2%.[23]

In a 10-year audit of 623 fetuses referred for fetal ECG in the Netherlands, 301 (48%) had some form of cardiac pathology. CHDs, usually severe, were seen in 81%, 26% of which had chromosomal abnormalities. In the CHD cases with normal karyotypes, 23% had extracardiac anomalies. There were terminations of pregnancy in 24% and a further 19% were intrauterine or postnatal deaths. The termination of pregnancy rate was 24.9% for all cardiac pathology and was 29.6% for the severe CHD group. Once first trimester nuchal translucency screening as an indication for increased cardiac risk was introduced in this Dutch population, referral for fetal ECG increased. Severe CHD was found in 34% (81/239) of fetuses with an increased nuchal translucency.[24]

OROFACIAL CLEFTS: PRESENT SCREENING PERFORMANCE

Although the majority of orofacial clefts (OFCs) are not detected prenatally, routine and enhanced ultrasound techniques can be valuable for assessing fetuses at risk. Sommerlad et al.[25] used a conventional 2D ultrasound combined with an enhanced 3D technique to evaluate fetal lips,

alveolar ridge, and secondary palate in 100 fetuses suspected of having an isolated OFC on standard ultrasound. The sensitivity for cleft lip diagnosis was 95% with a false positive rate (FPR) of 7.7%; for alveolar ridge clefts, sensitivity was 4.5% with a FPR of 7.2% and for hard palate clefts, sensitivity was 89.7% with a FPR of 15.6%. The authors concluded that this ultrasound technique was feasible in 90% of patients and correctly identified the nature of the OFC in 90% of cases.

Mailath-Pokorny et al.[26] studied the added value of MRI in prenatal diagnosis of OFCs. Thirty-four women had a fetal MRI at a mean of 26 weeks gestation (range 19–34 weeks) after ultrasound had identified either a facial cleft (N=29) or other malformation (N=5). MRI successfully visualized OFCs in both primary and secondary palates and allowed classifications that correlated with postnatal examination in all 34. Ultrasound imaging had missed five OFCs and misclassified 15 others.

LIMB ANOMALIES: PRESENT SCREENING PERFORMANCE

Although careful ultrasound examination of the limbs can detect deficiency defects, most are not routinely identified prenatally (approximately 25% of isolated cases and roughly 45% with other CAs).[27]

With respect to multiple contractures (i.e., arthrogryposis), prenatal evaluation including imaging (e.g., ultrasound, MRI), cytogenetic and molecular/microarray testing and serial fetal surveillance for hydrops and polyhydramnios can be helpful.[28] Delivery planning can be assisted by using MRI and ultrasound to predict pulmonary hypoplasia (e.g., secondary to kyphosis and/or scoliosis) or potential problems for resuscitation or intubation (e.g., secondary to jaw or spinal features).

Ultrasound features that aid early evaluation for skeletal dysplasia include increased nuchal translucency, short femora, abnormal skull shape or mineralization, facial profile and chest shape. Assessment is problematic before the second trimester. In fifteen cases where a diagnosis of skeletal dysplasia had been suspected by 14 weeks gestation, retrospective evaluation determined that accurate prenatal diagnosis was made only in those cases with positive family history and in single de novo cases of thanatophoric dysplasia and Roberts syndrome.[7]

Fetal talipes (i.e., club foot) is a relatively common finding on ultrasound. Sharma et al.[29] reviewed 174 prenatally diagnosed cases of talipes equinovarus and classified them as isolated (47.7%) or complex with other CAs (52.3%). Outcomes were poor when other anomalies were present and a high frequency of cases had CNS anomalies and/or abnormal karyotypes. The isolated cases did better, but the preterm birth rate was high (18%), potentially due to the high proportion of multiple pregnancies (19%).

GASTROSCHISIS / ABDOMINAL WALL DEFECTS: PRESENT SCREENING PERFORMANCE

A retrospective review of 113 cases determined that prenatal ultrasound diagnosis tends to be more accurate for omphalocele (91%) than for gastroschisis (79%).[30] In gastroschisis, there is usually an isolated defect and increased MSAFP. Omphalocele cases are more likely to have other CAs such as cardiac defects (18–24%), chromosomal anomalies (more typical with smaller defects), pulmonary hypoplasia (associated with "giant" omphaloceles), Central Nervous System (CNS) anomalies and atypical VACTERL association.

SUMMARY

Prenatal identification of congenital anomalies uses maternal evaluation (e.g., whole blood, serum, molecular analysis, carrier screening, genetic molecular mutation analysis, fetal molecular analysis) and fetal imaging (e.g., ultrasound, MRI, CT scan) for evaluation of the conceptus and its development. Major CAs amenable to prenatal diagnosis include aneuploidy, NTDs and other CNS defects, CHDs, respiratory anomalies, abdominal wall defects, renal anomalies, limb anomalies, OFCs and pathology secondary to monochorionic twinning.

Fetal therapy has a place for improving fetal mortality and neonatal morbidity, but complete amelioration of the anomaly and its effects has not been reported. Maternal transfer for optimal fetal/neonatal care at designated tertiary centres for

further investigation, as well as counselling and ongoing expectant management and delivery should be considered as prenatal diagnosis can optimize outcomes after neonatal surgery for CAs such as congenital lung malformations, sacrococcygeal teratoma, myelomeningocele, giant fetal neck masses, diaphragmatic hernia and congenital heart defects.[31] After prenatal diagnosis of congenital anomalies, some parents will opt for termination of pregnancy. Regardless of the outcome, identification of an affected fetus and subsequent investigations into cause can allow for genetic counselling and facilitate plans for future pregnancy, including planned prenatal assessment or use of assisted reproductive technology.

Evaluation of prenatal testing in Canada indicates that many healthcare systems have limitations in providing state-of-the-art screening and diagnosis services due to cost. Issues with respect to the need for genetic counselling and informed consent, language barriers and distance from tertiary centres increases the barriers to access and availability. Despite these drawbacks, prenatal diagnosis and screening tests have clear economic benefit. Current standards of care dictate that such tests should be offered to all pregnant women to assess their risk of having a baby with a CA or genetic disorder.[19,31,32]

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CHAPTER 10

MANAGEMENT AND OUTCOMES IN OROFACIAL CLEFTS, DOWN SYNDROME AND SPINA BIFIDA

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This chapter deals with three common congenital anomalies, namely orofacial clefts, Down sydrome and spina bifida. We present some of the relevant points of management, prognosis and quality of life issues that affected individuals experience after birth.

OROFACIAL CLEFTS

Most orofacial clefts (OFCs) fall into two main groups: cleft lip with or without cleft palate (CL±CP), of which isolated cleft lip (CL) and cleft lip with cleft palate (CLP) are subgroups and cleft palate alone (CP). OFCs may be seen in isolation or associated with a syndrome, chromosomal anomaly or other malformation. The prognosis and management for each group will be very different depending on whether the cleft is an isolated anomaly or belongs to one of the other groups. Here we discuss the problems and issues related to the isolated examples of CL, CLP and CP. It is important to remember that a person with an isolated cleft may in fact belong to a less obvious syndrome group such as 22q11 deletion. Etiologic heterogeneity is a major factor in OFCs.

The major pediatric medical issues, including early feeding problems, recurrent ear infections often requiring insertion of tubes in the middle ear, conductive hearing loss, speech and language problems and complex dental problems, are well known and are covered very fully by Smyth.[1] He also discusses the pros and cons of different surgical methods or techniques and the timing of these, noting that surgery is best done with a team approach in a major centre. In Canada, most provinces will have such a team in place, but smaller provinces and the territories will likely require the services of adjoining provinces. Dental and orthodontic care may not be available through the Canadian universal healthcare system, especially after age 18.

QUALITY OF LIFE

There is increasing interest and concern regarding quality of life (QOL) and health related quality (HRQ) issues for persons living with congenital anomalies, especially when defects are visible. The latter can cause stigmatization, lack of self-esteem and psychosocial issues, especially in elementary school where conformity and sameness are important, but many of these same issues are still a problem for adults with OFCs.

Marcusson et al.[2] evaluated QOL in 68 adults with repaired CLP by means of a self-administered questionnaire, and compared them to 66 adults without clefting, matched for gender and age. The CLP group felt that their handicap had a marked effect on their lives, particularly on their overall well-being and social life. Mani et al.[3] studied 86 adults with unilateral CLP for a mean follow up time of 35 years and compared selected HRQ issues with normative data matched for age and gender. The patient group had lower values in the mental health category, but were similar to the controls in many other areas, indicating that most of the affected adults in their study appeared to cope well with their malformation. Ramstad et al.[4] investigated 233 Norwegian adults with a mean age of 28 years (range 20–35 years) with repaired CLP and compared them to a large control sample of similar age. Common psychological and medical problems among the CLP subjects were appearance, dentition and speech. Questions that yielded significant

differences between controls and persons with CLP were related to work, friendship and geographic mobility. Men seem to adjust less well than women indicating a need for psychologic counselling and psychiatric care from the craniofacial team. A follow-up study of 6,464 patients with clefting in Denmark (born 1936–1987)[5] found that 284 (4.4%) were hospitalized at some time for psychiatric disease, largely because of mental handicap and substance abuse. This increase in risk was not due to associated malformations or anomaly syndromes. The risk for schizophrenia and bipolar disorder was not significantly different from that of the general population.

Providing a syndromic form of CLP or CP has been excluded, the risk for the offspring of an affected person is in the 2–5% range (2% for CP, 2–5% for CL±CP with some evidence to suggest the higher risk for the offspring of a person with bilateral CLP and a lower one for unilateral CL). The risks may be higher if there is a positive family history for CLP or CP and genetic counselling advice should be sought. Prevention as a result of folic acid fortification or by pre- or post conceptional ingestion of multivitamins and folic acid has not been proven to change either first occurrence or recurrence. Prenatal diagnosis by ultrasound examination can be achieved (see Chapter 9).

MORTALITY

Early studies[6,7] found a higher infant mortality, especially when there were associated anomalies. However, even in isolated defects, the death rate was four times higher for CL±CP and 1.5 times higher for CP compared to that for infants with no anomalies.[7] In Denmark, a long term survival study[8] was conducted involving 5,331 persons with isolated CLP, who were born between 1943 and 1987 and followed to 1998. The expected number of deaths was 259, but 402 occurred, corresponding to a Standardized Mortality Ratio (SMR) of 1.4 for males and 1.8 for females. The increased risk of mortality was nearly constant for the three age intervals: first year of life, 1–17 years, 18–55 years. Death from cancer was only marginally increased, but the risk of suicide was significantly higher in both sexes. Accidents, which in some cases may be suicides, were not increased. About 50% of the overall deaths were attributed to causes other than the malformation. Deaths in the first year of life were due to prematurity, pneumonia, operative complications, asphyxia, aspiration, sepsis and an unknown group. For all other age groups, all but diseases of the central nervous system (CNS) showed moderate but non-significant increases in SMR. Mortality due to diseases of the CNS showed a significant increase for females. Stratifying for CL, CLP and CP, there was a significant risk for CLP and CP as compared to CL where there was only a slight risk of increased mortality.

COGNITIVE/LEARNING

Children with non-syndromic OFCs have been shown to have cognitive difficulties compared with matched controls, with many having language disabilities.[9,10] A study from Sweden[11] compared the intelligence of 17–19 year-old men with CL±CP (N=307) or CP (N=81) being evaluated for military service, with controls (N=272,879). Both groups were non-syndromic. Those with CL±CP showed no significant difference compared with the control group, but the CP group had significantly lower general intellectual scores. A quantitative MRI analysis of brain structure[12] found significant abnormalities in the brain morphology in adult males with non-syndromic CL±CP compared to a matched healthy control group. The abnormalities were: abnormally enlarged anterior regions of the cerebrum; decreased volume of the posterior cerebrum and cerebellum, with the left temporal lobe being severely affected. The structural abnormalities were directly related to cognitive function.

SUMMARY

Wherever possible, care and management for persons with OFCs is best managed by a comprehensive team in a major setting and should

extend beyond the pediatric age group. Psychological care—comprehensively reviewed by Kapp-Simon[13]—is an important part of the team to help such individuals adjust to life with their disability, particularly those with a visible defect. Unfortunately, appropriately specialized psychological care may not always be available. Accessing orthodontic and dental care may present a further challenge for adults, due to the fact that it is generally not covered for people over the age of 18.

Clearly, further research is needed to study the problems of brain abnormality and function. The decreased longevity, even in the absence of other anomalies, remains unexplained.

DOWN SYNDROME

Down syndrome (DS) results from extra chromosome 21 material in the genome.[14,15] DS is most often due to a non-familial chromosome imbalance as a result of maternal meiotic non-disjunction leading to trisomy 21. In about 5% of cases, it is the result of a translocation, usually involving a Robertsonian translocation with fusion between two acrocentric chromosomes; a chromosome 21 and most commonly a chromosome 14. About half of these are inherited translocations. Approximately 2% of persons with DS may have two cell lines (mosaicism); a normal cell line and a trisomy 21 cell line in various proportions. This usually results in a less severe phenotype and often a better outcome. Testing persons suspected of having DS involves taking a blood specimen for chromosome analysis; these tests are available in most major medical centres in Canada. Prenatal screening and diagnosis for DS is available in most major medical centres. This topic is covered in the chapter on prenatal diagnosis (see Chapter 9).

A variety of congenital anomalies and medical complications are more common in persons with DS (Table 10.1). There are anticipatory guidelines and health supervision guidelines by age categories that care givers can use to monitor health in persons affected by DS.[16] Resources and support for parents of children with DS are available through provincial and national DS support groups or associations and through various web sites.

TABLE 10.1

Common health concerns in children with Down syndrome*

Condition	% Affected
Hearing loss	75
Visual impairment	60
Sleep apnea	50–75
Congenital heart disease	40–50
Transient myeloproliferative disorder	10
Gastrointestinal atresia	12
Thyroid disease	4–18
Seizures	1–13
Coeliac disease	5
Atlantoaxial instability	1–2
Autism	1
Hirschsprung disease	<1
Leukemia	1

* Modified from Bull, 2011[16]

Telling new parents about the diagnosis of DS is a sensitive issue and one that requires knowledge, skill, sensitivity and compassion.[17,18] For future pregnancies, affected parents should be advised that the recurrence risk of DS is higher than in the general population. They should also be referred for genetic counselling. Precise risk calculation will depend on the mother's age in previously-affected and subsequent pregnancies. For translocation carriers, the risk is higher if the mother is a carrier than if the father carries the translocation (10–15% vs. 1–2%).[19,20]

INTERVENTIONS AND QUALITY OF LIFE

Medical complications do not usually dominate care and, barring major medical issues such as congenital heart defects, caring for a child with Down syndrome is not much different from caring for any other child. Persons with DS need love, care and respect like any other person. A balanced perspective, with hope and encouragement, and discussion of positive aspects can promote parents' adaptation to the diagnosis and encourage an attitude and perspective of acceptance and normalization.

Since most children with DS are delayed in reaching most developmental milestones, early intervention that includes speech therapy, occupational therapy, and physical therapy is recommended. There is evidence that these interventions can optimize long-term outcomes.[21,22] At school age, individualized education plans can be tailored to the child's needs, which typically involve a special education classroom setting. Inclusion in school can result in improved social skills, speech and language, literacy, daily living skills and behaviour. [23] Older children with DS have a lower QOL and HRQ when compared to children at the same age.[24] This often manifests as emotional and behavioural problems and significantly lower gross motor skills, autonomy, social functioning and cognitive functioning.[25]

People with DS have wide ranges of abilities, ranging from nonverbal individuals to those who are high-functioning. They require different levels of support as adults. Higher-functioning adults with DS can participate in social, physical, educational, and vocational activities.[26] Some of these young adults are able to live outside of the primary household, obtain a driver's license, get married and be gainfully employed. Individuals with mild intellectual disability may go on to attend post-secondary schooling. Fertility is reduced in adults with DS. Males are almost always infertile due to defects in spermatogenesis. However, there are a few reports of males with DS fathering a child. Women with DS are at increased risk of having offspring with DS. The risk is less than the theoretical risk of 50% due to the higher loss rate of trisomic embryos and fetuses. Prenatal diagnosis has been discussed in Chapter 9.

Mental illness occurs in approximately 30% of all adults with DS with depression being the most frequent. Common symptoms of depression in DS include sleep and behaviour disturbances, apathy, and weight change.[27] Other health issues common to adults with DS include obesity, osteoporosis, and lower cardiovascular fitness.[25] Exercise programs appear to positively affect the overall health of adults with DS, thereby increasing the quality of life and years of healthy life for these individuals.[26]

Almost all adults with DS over 40 years of age display neuropathology consistent with Alzheimer disease. Prevalence rates for Alzheimer disease among adults with DS increase with age, with rates of 10% at 30–39 years, up to 55% at 50–59 years and almost 75% at 60–65 years.[28]

MORTALITY

Many persons with DS are living longer due to medical interventions and improvements in treatment of congenital anomalies. The estimated life expectancy of people with DS in developed countries has increased from an average of 12 years in the 1940s to a current average of 57.8 years for women and 61.1 years for men.[29,30]

Data from Western Australia indicate that 6.5% of infants with DS born between 1980–2004 died within the first year. However, while the infant mortality rate between 1980–1984 was 13%, this had dropped to 4% by 2000–2004. There is a strong correlation between the presence of congenital heart defects and death during the first 10 years of life, with improved survival correlated with earlier

surgical correction of the congenital heart disease.[29] In adults over 40 years, pneumonia and other respiratory infections were the most common causes of death (39.6%), followed by coronary artery disease (9.9%), cardiac, renal, and respiratory failure (9%), cerebrovascular accident (6.3%), and cancers (5.4%).[29]

SUMMARY

DS remains a common condition that is associated with a high morbidity and mortality. Improved care and intervention has resulted in an improved quality of life and enhanced survival with increasing longevity for many persons affected by DS. Despite these improvements, the burden of this chromosomal imbalance does remain substantial in terms of physical and mental health challenges, both to those affected and those caring for these vulnerable members of our society.

SPINA BIFIDA

The prevalence of spina bifida congenita (SBC) and all forms of neural tube defects has decreased in the past 20 to 30 years likely because of periconceptional folic acid supplementation, food fortification in several countries, and prenatal screening for fetal anomalies. SBC results from the failure of closure of the neural tube between 21 and 28 days post conception. The reasons for this are unclear, but most of these defects are due to multifactorial inheritance in which both genetic and environmental factors are operating. One important environmental factor is folic acid which has been shown to substantially, but not completely, reduce the risk of occurrence of SBC and related neural tube defects. Optimal use of preconceptional folic acid, decreases recurrence risks from 3.5% to 1%, an over 70% reduction. SBC can be a feature of a child with multiple anomalies (syndromic forms) or can occur as an isolated birth defect. Syndromic forms include chromosomal disorders (e.g., trisomy 13 or 18), teratogenic conditions (e.g., valproic acid embryopathy, diabetic embryopathy), and other genetic (e.g., Currarino syndrome) or multiple congenital anomalies disorders (e.g., OEIS complex, pentalogy of Cantrell). This discussion will be restricted to non-syndromic forms of SBC.

CLASSIFICATION

SBC and other forms of spinal dysraphism can be open or closed defects. The clinical effects of SBC depend in part on the severity of the lesion and the location. The reader is referred to an excellent review article on classification and imaging characteristics of SBC.[31]

MANAGEMENT, COMPLICATIONS AND QUALITY OF LIFE

Although there is no clear evidence from the neurosurgical perspective to favour caesarean section in the absence of gross hydrocephalus, breech presentation or other obstetric indications,[32] many children with a prenatal diagnosis of SBC are delivered in this way. Optimally, the back lesion should be closed within 72 hours after birth. Doing so further decreases the risk of CNS infection and possibly improves neurological outcome. Prophylactic antibiotics may be associated with a lower risk of ventriculitis. Surgical treatment will not be addressed further here and readers are referred to a review article for more details.[32]

Approximately 80–90% of individuals with SBC will develop hydrocephaly. Many are shunted at the time of meningomyelocele repair. In the absence of obvious hydrocephalus, monitoring of ventricular size is common practice. Where there is only moderate enlargement the decision to shunt may be deferred. Placement of a shunt imposes a significant burden to children with the risk of ventriculitis and need for shunt revision. Shunt dependent hydrocephalus and shunt related complications are not only detrimental to cognitive outcome, but are strongly related to reduced survival.[33]

Urinary tract infections are common in SBC. They are more frequent in lumbosacral level lesions than in other locations. The introduction of clean intermittent catheterization, the use of anticholinergic drugs to improve bladder capacity and aggressive management of constipation have significantly improved the urological prognosis both in terms of reducing the risk of renal damage and reduction in the number of infections.[34, 35] Many patients can be managed with clean intermittent

catheterization, but some will require incontinent urinary diversion, such as vesicostomy, ileovesicostomy or ileal conduit creation.[34]

Children born with SBC have reduced life expectancy and suffer significant cognitive and physical disability, remaining wholly or partially dependent on the care of others into adult life.[35,36] Spinal deformities and scoliosis are also seen in a minority of adolescent and adult patients with SBC and sometimes require surgical treatment with spinal fusion.[37]

Tethered spinal cord may be a primary defect in some forms of spinal dysraphism or can occur after surgical repair of the spinal defect. Following the initial surgery, the terminal spinal cord remains low in the spinal canal, commonly imbedded in scar tissue. As spinal growth continues, traction is exerted on the spinal cord and nerve roots leading to ischaemic injury, and secondary neurological deterioration including pain, decreased motor function and foot deformities. Once recognized, surgical repair can reverse this process.

Severe developmental delay is seen in about 15% of patients with SBC.[31] Otherwise, the prospects for independent mobility are strongly related to the neurological level of the lesion. For low lumbar and sacral lesions, independent mobility is expected. For lesions above the second lumbar vertebra, loss of quadriceps and iliopsoas muscle function means that independent mobility is unlikely and will result in reliance on a wheel chair.[38] Approximately 70% of patients with SBC will have an IQ of 80 or more.[39] What limited data are available on adult survivors suggest that between 25–38% will be gainfully employed.[40]

Most males and females with SBC are fertile. Males may have more difficulty fathering children due to problems achieving erection and ejaculation rather than lack of fertility. The recurrence risk to offspring born to a parent with SBC is in the 3-4% range regardless of the gender of the affected parent, but can be significantly reduced by preconception folic acid supplementation. Prevention and prenatal diagnosis have been discussed fully in Chapters 8 and 9.

SURVIVAL

In the absence of additional serious congenital anomalies, individuals born with SBC are now likely to survive for an average of 30 years.[41,42] Ventriculitis and shunt related complications were the prime causes of death during infancy in the past; however, brainstem dysfunction (due to Chiari II malformation) leading to respiratory impairment and swallowing dysfunction now explains the majority of early deaths.[43,44]

SUMMARY

Spina bifida is considered one of the most complex birth defects compatible with life. Individuals with SBC suffer from brain complications, spinal cord injury and compromised renal function. Children and adults with SBC need multiple specialists, generalists who can address health promotion, and an integrated system to deliver this complex care. Improved care has resulted in improved QOL and survival; better preventive strategies have reduced the number of children born with this complex condition.[45,46]

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CONCLUSION

PRECONCEPTION HEALTH AND CONGENITAL ANOMALIES SURVEILLANCE IN CANADA: MEETING CANADA'S FUTURE HEALTH NEEDS

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One of the main goals of public health is to improve the health and well-being of populations by means of health promotion and primary prevention. As a perinatal health outcome, congenital anomalies impact 3–5% of infants in Canada, and are a major contributor to infant mortality, premature births and childhood morbidity. Moreover, they often continue to have an impact on health and longevity well into adulthood. Thus, concerted efforts to promote preconception health across all levels of public health would yield dividends in protecting and improving population health.

> Health promotion and prevention of adverse perinatal health outcomes are most effective before conception.

Preconception interventions and practices have been described throughout this report and include:

- *Optimal nutrition, including folic acid fortification and supplementation;*
- *Maintenance of healthy preconception weight;*
- *Avoidance of alcohol, tobacco, street drugs and other known teratogens;*
- *Preconception control of maternal chronic diseases such as epilepsy and diabetes mellitus;*
- *Full immunization coverage; and,*
- *Avoidance, or reduction of medication use and exposure to suspected environmental teratogens.*

In current dollars, total annual health expenditures in Canada are approaching 200 billion dollars; of which hospitals costs make up the largest category.[1] Limiting our attention to acute management and treatment of congenital anomalies would simply contribute to these costs and place increasing pressure on our healthcare system in the long term. A primary prevention approach focusing on early intervention to offset the economic burden of these conditions makes sense. The introduction of mandatory folic acid fortification in 1998 by the Canadian government and the subsequent 46% reduction in the prevalence of neural tube defects nationwide represents the most notable preconception primary prevention strategy.[2] Thus, a new era of opportunities in preconception health promotion and primary prevention is upon us.

Shifting population demographics, chronic disease patterns, emerging genetic and reproductive technologies, and changes in the physical environment are variably influencing occurrence patterns of congenital anomalies in Canada and worldwide. These and other factors will continue to re-shape our understanding of congenital anomalies and prompt us to adapt our existing public health strategies accordingly. A broadened view of perinatal health considering determinants, outcomes and preconception health promotion, particularly for vulnerable populations in Canada, will remain important if we are to further elucidate the complex etiology of these conditions and successfully prevent them.

For these reasons, congenital anomalies are an important public health issue both nationally and internationally. In this respect, the World Health Organization (WHO) has urged member countries to:

- *record surveillance data on birth defects as part of national health information systems;*
- *develop expertise and build capacity in the prevention of birth defects and care of children with birth defects;*
- *strengthen research and studies on etiology, diagnosis and prevention of major birth defects and promote international cooperation in combating them and,*
- *collaborate with the International Clearinghouse for Birth Defects Surveillance and Research in order to improve collection of data on the global burden of mortality and morbidity due to birth defects.*[3]

The above WHO priorities align implicitly with the ongoing work of the Public Health Agency of Canada and its Canadian Congenital Anomalies Surveillance Network.

To meet Canada's future health needs in this area, there will be a continued requirement for national, provincial and territorial organizations involved in reproductive, maternal and infant health to ensure that public health strategies and programs are evidence-based and determined by appropriate priorities. This report serves to support that function and underscores the importance of integrating congenital anomalies surveillance and reproductive/preconception health promotion within the public health spectrum of priority setting, programming, practice and evaluation.

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APPENDIX A

HOW DATA FOR THE CANADIAN CONGENITAL ANOMALIES SURVEILLANCE SYSTEM (CCASS) ARE DERIVED

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SOURCES OF DATA

The majority of Canada's acute care hospitals forward data on all transfers, discharges or deaths to the Canadian Institute for Health Information (CIHI). This data are kept in CIHI's Discharge Abstract Database (DAD), which accounts for most hospital inpatient discharges in Canada. The province of Québec does not participate in the DAD, but their congenital anomalis (CAs) data are available via their Système de maintenance et d'exploitation des données pour l'étude de la clientèle hospitalière (MED-ÉCHO), which is very similar to the DAD.

The MED-ÉCHO system does not include stillbirths, requiring the Québec system to rely on vital statistics data to capture stillbirths with CAs. These only capture the cause of death, which limits the incidence of congenital anomalies in stillbirths as the cause of death is often not recorded as due to a CA, even when one is present. The DAD can also report several CAs in stillbirths while Vital Statistics is only able to report one. Up to 2007, data from Alberta were available to CCASS directly from the Alberta Congenital Anomalies Surveillance System (ACASS), a province-wide registry with multiple sources of ascertainment. Because more recent Alberta data are available through ACASS and the DAD (up to 2009), this report utilized these data sources. Authors selected the source according to the analysis needs for their chapters.

Each DAD data file contains demographic, health services and diagnoses information. Diagnosis information is managed using the International Classification of Diseases (ICD) codes (ICD-9 CM (Clinical Modification), or ICD-9 prior to 2001, and ICD-10-CA (Canadian Enhancement) from 2001 onwards. The implementation of ICD-10-CA across Canadian jurisdictions was completed in 2006. Demographic information includes variables such as province of residence, scrambled health insurance number, three-digit postal code, residence code, year of birth, gender, admission date, discharge date, date of death, birth weight, live birth or stillbirth, and 25 ICD codes.

MED-ÉCHO and ACASS data are merged with the CIHI-derived DAD data by the Maternal and Infant Health Section, Public Health Agency of Canada to create the final CCASS database.

ASCERTAINMENT

The CCASS data are limited to live births and stillbirths. The length of ascertainment changed from one year to 30 days in 2001 for all data derived from the DAD, due to administrative reasons.

The CCASS data using DAD depend on a melding process to group the admission of the same infant into one record to avoid duplication of CAs. This is a two-step approach. The first step is based on the melding of infant records using the scrambled health insurance number provided in the DAD, the second step involves a probabilistic method using CA codes, province of residence, birth date (only available for an infant up to 30 days), gender,three-digit postal code and a residence code that identifies the area in which the patient resides. Such codes are defined by the provincial and territorial Ministries of Health and may reflect city, municipality, health region, etc.

CODING OF CONGENITAL ANOMALIES

Categorization of congenital anomalies in CCASS includes summary by individual ICD codes, 59

standard categories and 14 major categories, see Table A.1. Minor CAs may fall under these codes, but are not included in the statistics. Anomalies which are not reported in major categories include: congenital anomalies of eyelids, lacrimal system, and orbit (743.6/Q10.0–Q10.6); certain musculoskeletal deformities of skull, face and jaw (754.0/Q67.0–Q67.4); other anomalies of larynx, trachea, and bronchus (748.3/Q31–Q32); other anomalies of intestine (751.5/ Q43.4–Q43.9); atresia and stenosis of urethra and bladder neck (753.6/ Q64.2–Q64.3); undescended testicle (752.5/Q53); other specified anomalies of skin (757.3/Q81, Q82.1–Q82.8); tongue tie (750.0/Q38.1). Individual counts of these codes can be obtained.

A CA category is defined by a list of one or more ICD codes. The CA category includes every infant with one or more of the codes listed within a given category. For example, an infant with an upper limb deficiency and a lower limb deficiency is counted as one case of limb deficiency. However, the upper and lower limb anomalies can also be reported as two separate categories, when needed, because they have two distinct ICD codes. Similarly, infants with more than one anomaly involving different categories will be counted in each of those categories as a case. For instance, an infant with cleft lip and palate and an atrioventriculoseptal defect will be counted as one case in each category.

Counting is straight forward when an anomaly and a case are one and the same, (e.g., gastroschisis, Down syndrome, cleft palate). However, when organs are paired, information is lost by grouping them under one category. For example, an infant with microphthalmia in one eye and glaucoma in the other (i.e., anomalies in two different sections of the eye), will only be counted once as a case of eye anomalies in CCASS. However, because microphthalmia (ICD-Q11.2) and glaucoma (ICD Q15.0) have separate ICD codes the two conditions can be reported separately, when the major categories are expanded.

Neural tube defects (NTDs) are a special case. Many systems such as the ACASS code only the highest level lesion, thus anencephaly will usually trump all other lesions; if two NTDs are present, a hierarchical decision is made by the ACASS coders (e.g., an infant has anencephaly and spina bifida, only anencephaly is coded and counted). The CCASS does not use this approach with respect to NTDs. This is not a problem when reporting NTDs as a category but could have an impact on the rates of anencephaly, encephalocele and spina bifida when reported separately.

STRENGTHS

- The CCASS provides national coverage.
- The timing of the availability of the DAD data continues to improve.
- The CCASS makes a very efficient use of available resources.
- Gestational age is available for the data reported in the DAD using the ICD-10-CA. Gestational age was not used in this report because this information is incomplete or non-existent prior to 2007.
- Since the use of ICD-10-CA data, the DAD allows for maternal and newborn linkage, which makes possible to include other important maternal variables (e.g., smoking, diabetes, hypertension, obesity and maternal age).

DATA LIMITATIONS

- Data from ACASS and MED-ÉCHO are ICD code-based and are processed in the same manner as CIHI DAD data by CCASS. Despite being processed in the same manner, certain rules may differ between systems as noted in the NTDs the rule of the highest level lesion example above.
- Coding is dependent on hospital coders who may utilize different coding protocols and who may have differing degrees of knowledge and skill concerning CA coding.
- Two specific issues relate to coding. First, because gestational age is not available, there may be grossly exaggerated rates of patent ductus arteriosus, patent foramen ovale, pulmonary hypoplasia and undescended testes. Although, as mentioned earlier, undescended testes are omitted as a

minor anomaly, data on them as an individual CA can be tabulated. Second, coding the individual components of a tetralogy of Fallot (e.g., pulmonary stenosis, VSD, and dextroposed aorta), will artificially inflate the rates of these CAs if they are considered individually. This would not represent an issue if this combination is reduced to a single category.

- The lack of information on terminations of pregnancy for CAs before 20 weeks gestation is a major weakness.
- Other limitations include lack of verification of diagnosis, no follow-up on apparent clusters, inability to totally eliminate duplications and lack of information on maternal or paternal risk factors.

TABLE A.1

Canadian Congenital Anomalies Surveillance System Routine Analysis Categories

Categories	ICD-9 Codes	ICD-10 Codes
Births		
Stillbirths		
Neural tube defects		
Anencephalus & similar anomalies	740.0–740.2	Q00.0–Q00.2
Spina bifida	741.0–741.9	Q05.0–Q05.9, Q07.0
Encephalocele	742.0	Q01.0–Q01.2, Q01.8, Q01.9
Central nervous system anomalies		
Anencephalus & similar anomalies	740.0–740.2	Q00.0–Q00.2
Spina bifida	741.0–741.9	Q05.0–Q05.9, Q07.0
Encephalocele	742.0	Q01.0–Q01.2,Q01.8,Q01.9
Microcephalus & brain reduction	742.1–742.2	Q02, Q04.0–Q04.3
Congenital hydrocephalus	742.3	Q03.0, Q03.1, Q03.8, Q03.9
Other specified & unspecified CNS anomalies	742.4–742.9	Q04.4–Q04.6, Q04.8, Q04.9, Q06.0–Q06.4, Q06.8, Q06.9, Q07.8, Q07.9
Eye anomalies		
Anophthalmos, microphthalmos	743.0–743.1	Q11.0–Q11.2
Other eye anomalies	743.2–743.9	Q10.0–Q10.7, Q11.3, Q12.0–Q12.4, Q12.8–Q13.5, Q13.8–Q14.3, Q14.8–Q15.0, Q15.8, Q15.9
Ear face & neck anomalies		
Anomalies of ear causing impairment	744.0	Q16.0, Q16.1, Q16.3–Q16.5, Q16.9
Other ear anomalies	744.1–744.3	Q16.2, Q17.0–Q17.5, Q17.8, Q17.9
Anomalies of face & neck	744.4–744.9	Q18.0–Q18.9
Congenital heart defects		
Common truncus	745.0	Q20.0, Q21.4
Transposition of great vessels	745.1	Q20.1–Q20.3, Q20.5
Tetralogy of Fallot	745.2	Q21.3

Categories	ICD-9 Codes	ICD-10 Codes
Common ventricle	745.3	Q20.4
Ventricular septal defect	745.4	Q21.0, Q21.8
Atrial septal defect	745.5	Q21.1
Endocardial cushion defects	745.6	Q21.2
Other septal closure defects	745.7–745.9	Q21.9
Heart valve anomalies	746.0–746.6	Q22.0–Q22.5, Q23.0–Q23.3
Hypoplastic left heart syndrome	746.7	Q23.4
Other heart anomalies	746.8–746.9	Q20.6, Q20.8, Q20.9, Q22.6, Q22.8, Q22.9, Q23.8–Q24.6, Q24.8, Q24.9
Circulatory system anomalies		
Coarctation of aorta	747.1	Q25.1
Other anomalies of aorta	747.2	Q25.2–Q25.4
Pulmonary artery anomalies	747.3	Q25.5–Q25.7
Other circulatory system anomalies	747.4–747.9	Q25.8–Q26.6, Q26.8–Q27.4, Q27.8–Q28.3, Q28.8, Q28.9
Respiratory system anomalies		
Nose anomalies	748.0, 748.1	Q30.0–Q30.3, Q30.8, Q30.9
Lung agenesis & hypoplasia	748.5	Q33.2, Q33.3, Q33.6
Other respiratory system anomalies	748.2–748.4, 748.6, 748.8, 748.9	Q31.0–Q31.4, Q31.8–Q32.4, Q33.0, Q33.1, Q33.4, Q33.5, Q33.8–Q34.1, Q34.8, Q34.9
Orofacial clefts		
Cleft palate	749.0	Q35.0–Q35.9
Cleft lip	749.1	Q36, Q36.0, Q36.1, Q36.9
Cleft palate with cleft lip	749.2	Q37, Q37.0–Q37.5, Q37.8, Q37.9
Digestive system anomalies		
T-E fistula, esophageal atresia & stenosis	750.3	Q39.0–Q39.4, Q39.8
Other upper alimentary tract anomalies	750.1, 750.2, 750.4–750.9	Q38.0, Q38.2–Q38.8, Q39.5, Q39.6, Q39.9, Q40.0–Q40.3, Q40.8, Q40.9
Intestinal, anorectal atresia & stenosis	751.2	Q42.0–Q42.3, Q42.8, Q42.9
Other digestive system anomalies	751.0, 751.1, 751.3–751.9	Q41.0–Q41.2, Q41.8, Q41.9, Q43.0–Q44.7, Q45.0–Q45.3, Q45.8, Q45.9
Genital organ anomalies		
Hypospadias, epispadias	752.6	Q54.0–Q54.4, Q54.8, Q54.9, Q64.0
Other genital organ anomalies	752.0–752.5, 752.7–752.9	Q50.0–Q50.6, Q51.0–Q53.2, Q53.9, Q55.0–Q55.6, Q55.8–Q56.4
Urinary system anomalies		
Renal agenesis & dysgenesis	753.0	Q60.0–Q60.6
Cystic kidney disease	753.1	Q61.0–Q61.5, Q61.8, Q61.9
Other urinary system anomalies	753.2–753.9	Q62.0–Q62.8, Q63.0–Q63.3, Q63.8, Q63.9, Q64.1–Q64.9

Categories	ICD-9 Codes	ICD-10 Codes
Musculoskeletal anomalies		
Certain musculoskeletal anomalies	754.0–754.2, 754.4, 754.8	Q67.0–Q67.7, Q68.0–Q68.5, Q76.3
Congenital dislocation of hip	754.3	Q65.0–Q65.6, Q65.8
Clubfoot	754.5–754.7	Q66.0–Q66.9
Polydactyly, syndactyly	755.0–755.1	Q69.0–Q69.2, Q69.9–Q70.4, Q70.9
Limb deficiency defects	755.2–755.4	Q71.0–Q71.4, Q71.5, Q71.8–Q73.1, Q73.8
Other, unspecified limb anomalies	755.5–755.9	Q65.9, Q68.8, Q71.6, Q74.0–Q74.3, Q74.8, Q74.9
Anomalies of abdominal wall	756.7	Q79.2–Q79.5
Other musculoskeletal anomalies	756.0–756.6, 756.8, 756.9	Q67.8, Q75.0–Q75.5, Q75.8–Q76.2, Q76.4–Q78.6, Q78.8–Q79.1, Q79.6, Q79.8, Q79.9
Gastroschisis*		Q79.3
Anomalies of integument	757.0–757.9	Q80.0–Q80.4, Q80.8–Q81.2, Q81.8–Q82.5, Q82.8–Q83.3, Q83.8–Q84.6, Q84.8, Q84.9
Down syndrome	758.0	Q90.0–Q90.2, Q90.9
Other chromosomal anomalies		
Trisomy 13	758.1	Q91.4–Q91.7
Trisomy 18	758.2	Q91.0–Q91.3
Autosomal syndromes	758.3–758.5	Q92.0–Q93.9, Q95.0–Q95.5, Q95.8, Q95.9
Sex chromosome conditions	758.6–758.8	Q96.0–Q96.4, Q96.8–Q97.3, Q97.8–Q99.2
Other & unspecified anomalies	758.9, 759.0–759.9	Q85.0, Q85.1, Q85.8–Q86.2, Q86.8, Q87.0–Q87.5, Q87.8, Q89.0–Q89.4, Q89.7–Q89.9, Q99.8, Q99.9
Fetal alcohol syndrome	Not reportable	Q86.0
Cases		
All anomalies		

Source: Canadian Congenital Anomaly Surveillance System.
*Gastrochisis was not included as a separate condition in routine CCASS analysis using ICD-9.

APPENDIX B

DATA TABLES

TABLE B1.1

Total congenital anomaly (CA) rate, *Canada (excluding Québec),* 1998–2009*

Year	Total births**	Number of cases	Prevalence rate (95% CI) per 10,000 total births
1998	269,079	12,140	451.2 (443.2–459.3)
1999	265,746	11,909	448.1 (440.1–456.3)
2000	258,667	11,428	441.8 (433.7–450.0)
2001	263,350	12,126	460.5 (452.3–468.7)
2002	259,505	11,207	431.9 (423.9–439.9)
2003	264,981	10,994	414.9 (407.2–422.7)
2004	266,277	10,830	406.7 (399.1–414.5)
2005	269,530	10,837	402.1 (394.5–409.7)
2006	275,737	10,564	383.1 (375.8–390.5)
2007	286,098	10,799	377.5 (370.4–384.6)
2008	290,725	11,203	385.3 (378.2–392.5)
2009	292,312	11,260	385.2 (378.1–392.4)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2009.
*Québec was excluded because data were not available for all years. **Total births include live births and stillbirths.
CI—Confidence Interval

TABLE B1.2

Total congenital anomaly (CA) rate in live births, *Canada (excluding Québec),* 1998–2009*

Year	Live births	Number of cases	Prevalence rate (95% CI) per 10,000 live births
1998	267,386	11,804	441.5 (433.5–449.5)
1999	263,932	11,484	435.1 (427.2–443.1)
2000	256,943	11,053	430.2 (422.2–438.3)
2001	261,524	11,735	448.7 (440.6–456.9)
2002	257,634	10,802	419.3 (411.4–427.3)
2003	263,051	10,569	401.8 (394.2–409.5)
2004	264,305	10,446	395.2 (387.7–402.9)
2005	267,465	10,422	389.7 (382.2–397.2)
2006	273,680	10,114	369.6 (362.4–376.8)
2007	283,871	10,283	362.2 (355.3–369.3)
2008	288,458	10,691	370.6 (363.6–377.7)
2009	290,067	10,763	371.1 (364.1–378.1)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2009.
*Québec was excluded because data were not available for all years. CI—Confidence Interval

TABLE B1.3

Total congenital anomaly (CA) rate in stillbirths, *Canada (excluding Québec),* 1998–2009*

Year	Total stillbirths	Number of cases	Prevalence rate (95% CI) per 10,000 total stillbirths
1998	1,693	336	1,984.6 (1778.1–2208.6)
1999	1,814	389	2,144.4 (1936.6–2368.5)
2000	1,724	368	2,134.6 (1922.0–2364.2)
2001	1,826	392	2,146.8 (1939.5–2370.2)
2002	1,871	404	2,159.3 (1953.8–2380.5)
2003	1,930	425	2,202.1 (1997.7–2421.7)
2004	1,972	384	1,947.3 (1757.3–2152.1)
2005	2,065	415	2,009.7 (1821.0–2212.7)
2006	2,057	450	2,187.7 (1990.2–2399.4)
2007	2,227	516	2,317.0 (2121.4–2525.8)
2008	2,267	512	2,258.5 (2067.1–2462.9)
2009	2,245	497	2,213.8 (2023.4–2417.3)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2009.
*Québec was excluded because data were not available for all years. CI—Confidence Interval

TABLE B1.4

Percentage of stillborn congenital anomaly (CA) cases <750 g, *Canada (excluding Québec),* 1998–2009*

Year	Total stillborn cases	Total stillborn cases with known birth weight	Number of stillborn cases <750 g	Percentage of total stillborn cases <750 g	Percentage of total stillborn cases with known birth weight <750 g
1998	336	320	212	63.1%	66.3%
1999	389	377	276	71.0%	73.2%
2000	368	349	257	69.8%	73.6%
2001	392	378	259	66.1%	68.5%
2002	404	353	252	62.4%	71.4%
2003	425	368	279	65.6%	75.8%
2004	384	342	258	67.2%	75.4%
2005	415	370	286	68.9%	77.3%
2006	450	356	288	64.0%	80.9%
2007	516	387	286	55.4%	73.9%
2008	512	382	278	54.3%	72.8%
2009	497	383	285	57.3%	74.4%

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2009.
*Québec was excluded because data were not available for all years.

TABLE B1.5A/B

Total congenital anomaly (CA) rate, by province/territory, *Canada (excluding Québec),* 2000–2009 combined*

Province/territory	Total births**	Number of cases	Prevalence rate (95% CI) per 10,000 total births
Newfoundland and Labrador	46,294	2,880	622.1 (599.6–645.3)
Prince Edward Island	14,039	589	419.5 (386.3–454.8)
Nova Scotia	88,046	3,174	360.5 (348.1–373.3)
New Brunswick	70,791	3,148	444.7 (429.3–460.5)
Ontario	1,368,360	52,836	386.1 (382.8–389.4)
Manitoba	143,598	4,994	347.8 (338.2–357.6)
Saskatchewan	124,584	4,899	393.2 (382.3–404.4)
Alberta	430,089	20,168	468.9 (462.5–475.4)
British Columbia	409,270	16,806	410.6 (404.4–416.9)
Yukon	3,912	178	455.0 (390.6–527.0)
Northwest Territories	6,984	268	383.7 (339.2–432.5)
Nunavut	5,529	328	593.2 (530.8–661.0)
CANADA‡	2,727,182	111,248	407.9 (405.5–410.3)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 2000–2009.
* Québec was excluded because data were not available for all years. ** Total births include live births and stillbirths.
‡ Includes data for unknown provinces/territories. CI—Confidence Interval

TABLE B1.6

Total congenital anomaly (CA) rate, by gender, *Canada (excluding Québec),* 1998–2009*

Year	Total births**	Males			Females	
		Number of cases	Prevalence rate (95% CI) per 10,000 total births		Number of cases	Prevalence rate (95% CI) per 10,000 total births
1998	269,079	6,909	256.8	(250.7–262.9)	5,209	193.6 (188.4–198.9)
1999	265,746	6,629	249.4	(243.5–255.5)	5,227	196.7 (191.4–202.1)
2000	258,667	6,492	251.0	(244.9–257.2)	4,922	190.3 (185.0–195.7)
2001	263,350	6,734	255.7	(249.6–261.9)	5,383	204.4 (199.0–209.9)
2002	259,505	6,288	242.3	(236.4–248.4)	4,907	189.1 (183.8–194.5)
2003	264,981	6,187	233.5	(227.1–239.4)	4,794	180.9 (175.8–186.1)
2004	266,277	6,174	231.9	(226.1–237.7)	4,639	174.2 (169.2–179.3)
2005	269,530	6,118	227.0	(221.3–232.7)	4,693	174.1 (169.2–179.2)
2006	275,737	6,025	218.5	(213.0–224.1)	4,513	163.7 (158.9–168.5)
2007	286,098	6,071	212.2	(206.9–217.6)	4,682	163.7 (159.0–168.4)
2008	290,725	6,445	221.7	(216.3–227.2)	4,711	162.0 (157.4–166.7)
2009	292,312	6,532	223.5	(218.1–228.9)	4,678	160.0 (155.5–164.7)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2009.
*Québec was excluded because data were not available for all years. **Total births include live births and stillbirths.
CI—Confidence Interval

TABLE B1.7

Ratio of total male to total female congenital anomaly cases (CA), *Canada (excluding Québec),* 1998–2009*

Year	Number of male cases	Number of female cases	Ratio of male to female cases
1998	6,909	5,209	1.33
1999	6,629	5,227	1.27
2000	6,492	4,922	1.32
2001	6,734	5,383	1.25
2002	6,288	4,907	1.28
2003	6,187	4,794	1.29
2004	6,174	4,639	1.33
2005	6,118	4,693	1.30
2006	6,025	4,513	1.34
2007	6,071	4,682	1.30
2008	6,445	4,711	1.37
2009	6,532	4,678	1.40

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2009.
*Québec was excluded because data were not available for all years.

TABLE **B2.1**

Down syndrome (DS) rate, *Canada, 1998–2007*

Year	Total births*	Number of cases	Prevalence rate (95% CI) per 10,000 total births
1998	343,823	487	14.2 (12.9–15.5)
1999	338,407	492	14.5 (13.3–15.9)
2000	330,398	500	15.1 (13.8–16.5)
2001	336,835	449	13.3 (12.1–14.6)
2002	331,527	469	14.1 (12.9–15.5)
2003	338,417	507	15.0 (13.7–16.3)
2004	339,687	455	13.4 (12.2–14.7)
2005	347,476	517	14.9 (13.6–16.2)
2006	359,618	496	13.8 (12.6–15.1)
2007	372,724	483	13.0 (11.8–14.2)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1998–2007.
*Total births include live births and stillbirths. CI—Confidence Interval

TABLE B2.2A/B

Down syndrome (DS) rate, by province/territory, *Canada, 1998–2007 combined*

Province/territory	Total births*	Number of cases	Prevalence rate (95% CI) per 10,000 total births
Newfoundland and Labrador	46,644	74	15.9 (12.5–19.9)
Prince Edward Island	14,078	24	17.0 (10.9–25.4)
Nova Scotia	89,344	171	19.1 (16.4–22.2)
New Brunswick	72,161	105	14.6 (11.9–17.6)
Québec	748,444	838	11.2 (10.5–12.0)
Ontario	1,354,028	1,923	14.2 (13.6–14.9)
Manitoba	141,087	208	14.7 (12.8–16.9)
Saskatchewan	122,222	185	15.1 (13.0–17.5)
Alberta	416,281	556	13.4 (12.3–14.5)
British Columbia	406,580	715	17.6 (16.3–18.9)
Yukon	3,938	§	§
Northwest Territories	7,434	18	24.2 (14.3–38.3)
Nunavut	4,186	9	21.5 (9.8–40.8)
CANADA‡	3,438,912	4,855	14.1 (13.7–14.5)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1998–2007.
*Total births include live births and stillbirths. § Rate suppressed due to small cell counts (<5).
‡Includes data for unknown provinces/territories. CI—Confidence Interval

TABLE B3.1A

Neural tube defect (NTD) rate, *Canada, 1996–2007*

Year	Total births*	Number of cases	Prevalence rate (95% CI) per 10,000 total births
1996	366,811	278	7.6 (6.7–8.5)
1997	351,139	267	7.6 (6.7–8.6)
1998	343,823	194	5.6 (4.9–6.5)
1999	338,407	196	5.8 (5.0–6.7)
2000	330,398	170	5.1 (4.4–6.0)
2001	336,835	166	4.9 (4.2–5.7)
2002	331,527	145	4.4 (3.7–5.1)
2003	338,417	150	4.4 (3.8–5.2)
2004	339,687	130	3.8 (3.2–4.5)
2005	347,476	159	4.6 (3.9–5.3)
2006	359,618	126	3.5 (2.9–4.2)
2007	372,724	154	4.1 (3.5–4.8)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1996–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1996–2007.
*Total births include live births and stillbirths. CI—Confidence Interval

TABLE B3.1B

Spina bifida congenita (SBC) rate, *Canada, 1996–2007*

Year	Total births*	Number of cases	Prevalence rate (95% CI) per 10,000 total births
1996	366,811	200	5.5 (4.7–6.3)
1997	351,139	188	5.4 (4.6–6.2)
1998	343,823	142	4.1 (3.5–4.9)
1999	338,407	136	4.0 (3.4–4.8)
2000	330,398	110	3.3 (2.7–4.0)
2001	336,835	104	3.1 (2.5–3.7)
2002	331,527	98	3.0 (2.4–3.6)
2003	338,417	99	2.9 (2.4–3.6)
2004	339,687	84	2.5 (2.0–3.1)
2005	347,476	106	3.1 (2.5–3.7)
2006	359,618	86	2.4 (1.9–3.0)
2007	372,724	102	2.7 (2.2–3.3)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1996–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1996–2007.
*Total births include live births and stillbirths. CI—Confidence Interval

TABLE B3.1C

Anencephalus & similar anomalies rate, *Canada, 1996–2007*

Year	Total births*	Number of cases	Prevalence rate (95% CI) per 10,000 total births
1996	366,811	42	1.1 (0.8–1.5)
1997	351,139	54	1.5 (1.2–2.0)
1998	343,823	31	0.9 (0.6–1.3)
1999	338,407	31	0.9 (0.6–1.3)
2000	330,398	38	1.2 (0.8–1.6)
2001	336,835	39	1.2 (0.8–1.6)
2002	331,527	29	0.9 (0.6–1.3)
2003	338,417	33	1.0 (0.7–1.4)
2004	339,687	36	1.1 (0.7–1.5)
2005	347,476	33	0.9 (0.7–1.3)
2006	359,618	28	0.8 (0.5–1.1)
2007	372,724	30	0.8 (0.5–1.1)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1998–2007.
*Total births include live births and stillbirths. CI—Confidence Interval

TABLE B3.1D

Encephalocele rate, *Canada, 1996–2007*

Year	Total births*	Number of cases	Prevalence rate (95% CI) per 10,000 total births
1996	366,811	40	1.1 (0.8–1.5)
1997	351,139	33	0.9 (0.6–1.3)
1998	343,823	23	0.7 (0.4–1.0)
1999	338,407	31	0.9 (0.6–1.3)
2000	330,398	25	0.8 (0.5–1.1)
2001	336,835	26	0.8 (0.5–1.1)
2002	331,527	20	0.6 (0.4–0.9)
2003	338,417	25	0.7 (0.5–1.1)
2004	339,687	12	0.4 (0.2–0.6)
2005	347,476	25	0.7 (0.5–1.1)
2006	359,618	13	0.4 (0.2–0.6)
2007	372,724	23	0.6 (0.4–0.9)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1996–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1996–2007.
*Total births include live births and stillbirths. CI—Confidence Interval

TABLE B3.2A
Neural tube defect (NTD) rate, by province/territory, *Canada, 1991–1996 combined*

Province/territory	Total births*	Number of cases	Prevalence rate (95% CI) per 10,000 total births
Newfoundland and Labrador	37,383	114	30.5 (25.2–36.6)
Prince Edward Island	10,172	10	9.8 (4.7–18.1)
Nova Scotia**	10,623	21	19.8 (12.2–30.2)
New Brunswick	55,154	86	15.6 (12.5–19.3)
Québec	541,446	371	6.9 (6.2–7.6)
Ontario	897,664	849	9.5 (8.8–10.1)
Manitoba	98,184	98	10.0 (8.1–12.2)
Saskatchewan	80,865	96	11.9 (9.6–14.5)
Alberta	243,150	190	7.8 (6.7–9.0)
British Columbia	277,204	245	8.8 (7.8–10.0)
Yukon	2,717	§	§
Northwest Territories	7,633	§	§
Nunavut***	N/A	N/A	N/A
CANADA‡	2,251,572	2,063	9.2 (8.8–9.6)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1991–1996.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1991–1996.
*Total births include live births and stillbirths.
**Nova Scotia data from 1991–1995 were excluded as they were not available to CCASS prior to 1996.
***Territorial data was unavailable because Nunavut was not established as a territory until 1999. Data on births in Nunavut were included within those of the Northwest Territories. §Rate suppressed due to small cell counts (<5). ‡Includes data for unknown provinces/territories.
CI—Confidence Interval

TABLE B3.2B

Neural tube defect (NTD) rate, by province/territory, Canada, 1997–2000 combined

Province/territory	Total births*	Number of cases	Prevalence rate (95% CI) per 10,000 total births
Newfoundland and Labrador	20,426	17	8.3 (4.8–13.3)
Prince Edward Island	5,973	§	§
Nova Scotia	38,512	37	9.6 (6.8–13.2)
New Brunswick	31,591	23	7.3 (4.6–10.9)
Québec	295,660	161	5.4 (4.6–6.4)
Ontario	536,421	329	6.1 (5.5–6.8)
Manitoba	57,456	45	7.8 (5.7–10.5)
Saskatchewan	50,110	29	5.8 (3.9–8.3)
Alberta	151,960	71	4.7 (3.6–5.9)
British Columbia	169,658	115	6.8 (5.6–8.1)
Yukon	1,576	§	§
Northwest Territories	3,826	§	§
Nunavut**	598	§	§
CANADA‡	1,325,255	827	6.1 (5.7–6.5)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1997–2000.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1997–2000.
*Total births include live births and stillbirths.
**The rate for Nunavut is a combined rate for the 2-year period of 1999–2000 because Nunavut was not established as a territory until 1999.
§Rate suppressed due to low cell numbers (<5). ‡Includes data for unknown provinces/territories. CI—Confidence Interval

TABLE B3.2C

Neural tube defect (NTD) rate, by province/territory, *Canada, 2001–2007 combined*

Province/territory	Total births*	Number of cases	Prevalence rate (95% CI) per 10,000 total births
Newfoundland and Labrador	31,660	15	4.7 (2.6–7.8)
Prince Edward Island	9,675	§	§
Nova Scotia	60,849	31	5.1 (3.5–7.2)
New Brunswick	48,716	17	3.5 (2.0–5.6)
Québec	531,165	173	3.3 (2.8–3.8)
Ontario	954,653	386	4.0 (3.6–4.5)
Manitoba	98,386	54	5.5 (4.1–7.2)
Saskatchewan	84,577	42	5.0 (3.6–6.7)
Alberta	301,475	126	4.2 (3.5–5.0)
British Columbia	281,500	168	6.0 (5.1–6.9)
Yukon	2,817	§	§
Northwest Territories	4,738	§	§
Nunavut	3,588	§	§
CANADA‡	2,426,284	1,030	4.2 (4.0–4.5)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 2001–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 2001–2007.
*Total births include live births and stillbirths.
§Rate suppressed due to small cell counts (<5). ‡Includes data for unknown provinces/territories. CI—Confidence Interval

TABLE B4.1

Congenital heart defect (CHD) rate, *Canada (excluding Québec),* 1998–2009*

Year	Total births**	Number of cases	Prevalence rate (95% CI) per 10,000 total births
1998	269,079	2,883	107.1 (103.3–111.1)
1999	265,746	2,816	106.0 (102.1–110.0)
2000	258,667	2,902	112.2 (108.1–116.3)
2001	263,350	2,858	108.5 (104.6–112.6)
2002	259,505	2,681	103.3 (99.4–107.3)
2003	264,981	2,513	94.8 (91.2–98.6)
2004	266,277	2,626	98.6 (94.9–102.5)
2005	269,530	2,668	99.0 (95.3–102.8)
2006	275,737	2,583	93.7 (90.1–97.4)
2007	286,098	2,599	90.8 (87.4–94.4)
2008	290,725	2,751	94.6 (91.1–98.2)
2009	292,312	2,487	85.1 (81.8–88.5)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2009.
*Québec was excluded because data were not available for all years.
**Total births include live births and stillbirths. CI—Confidence Interval

TABLE B4.2A

Common truncus (CT) defect rate, *Canada (excluding Québec),* 1998–2009*

Year	Total births**	Number of cases	Prevalence rate (95% CI) per 10,000 total births
1998	269,079	39	1.4 (1.0–2.0)
1999	265,746	37	1.4 (1.0–1.9)
2000	258,667	33	1.3 (0.9–1.8)
2001	263,350	27	1.0 (0.7–1.5)
2002	259,505	17	0.7 (0.4–1.0)
2003	264,981	26	1.0 (0.6–1.4)
2004	266,277	13	0.5 (0.3–0.8)
2005	269,530	21	0.8 (0.5–1.2)
2006	275,737	17	0.6 (0.4–1.0)
2007	286,098	26	0.9 (0.6–1.3)
2008	290,725	27	0.9 (0.6–1.4)
2009	292,312	9	0.3 (0.1–0.6)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2009.
*Québec was excluded because data were not available for all years.
**Total births include live births and stillbirths. CI—Confidence Interval

TABLE B4.2B

Transposition of great vessels (TGV) rate, *Canada (excluding Québec),* 1998–2009*

Year	Total births**	Number of cases	Prevalence rate (95% CI) per 10,000 total births
1998	269,079	151	5.6 (4.8–6.6)
1999	265,746	167	6.3 (5.4–7.3)
2000	258,667	154	6.0 (5.1–7.0)
2001	263,350	116	4.4 (3.6–5.3)
2002	259,505	120	4.6 (3.8–5.5)
2003	264,981	112	4.2 (3.5–5.1)
2004	266,277	123	4.6 (3.8–5.5)
2005	269,530	135	5.0 (4.2–5.9)
2006	275,737	129	4.7 (3.9–5.6)
2007	286,098	130	4.5 (3.8–5.4)
2008	290,725	143	4.9 (4.1–5.8)
2009	292,312	149	5.1 (4.3–6.0)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2009.
*Québec was excluded because data were not available for all years.
**Total births include live births and stillbirths.
CI—Confidence Interval

TABLE B4.2C

Tetralogy of Fallot (TOF) rate, *Canada (excluding Québec),* 1998–2009*

Year	Total births**	Number of cases	Prevalence rate (95% CI) per 10,000 total births
1998	269,079	143	5.3 (4.5–6.3)
1999	265,746	130	4.9 (4.1–5.8)
2000	258,667	159	6.1 (5.2–7.2)
2001	263,350	105	4.0 (3.3–4.8)
2002	259,505	103	4.0 (3.2–4.8)
2003	264,981	96	3.6 (2.9–4.4)
2004	266,277	79	3.0 (2.3–3.7)
2005	269,530	118	4.4 (3.6–5.2)
2006	275,737	99	3.6 (2.9–4.4)
2007	286,098	102	3.6 (2.9–4.3)
2008	290,725	107	3.7 (3.0–4.4)
2009	292,312	93	3.2 (2.6–3.9)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2009.
*Québec was excluded because data were not available for all years.
**Total births include live births and stillbirths. CI—Confidence Interval

TABLE B4.2D

Endocardial cushion defect (ECD) rate, *Canada (excluding Québec),* 1998–2009*

Year	Total births**	Number of cases	Prevalence rate (95% CI) per 10,000 total births
1998	269,079	87	3.2 (2.6–4.0)
1999	265,746	87	3.3 (2.6–4.0)
2000	258,667	91	3.5 (2.8–4.3)
2001	263,350	65	2.5 (1.9–3.1)
2002	259,505	93	3.6 (2.9–4.4)
2003	264,981	94	3.5 (2.9–4.3)
2004	266,277	110	4.1 (3.4–5.0)
2005	269,530	110	4.1 (3.4–4.9)
2006	275,737	103	3.7 (3.0–4.5)
2007	286,098	101	3.5 (2.9–4.3)
2008	290,725	120	4.1 (3.4–4.9)
2009	292,312	121	4.1 (3.4–4.9)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2009.
*Québec was excluded because data were not available for all years. CI—Confidence Interval ** Total births include live births and stillbirths.

TABLE B4.2E

Hypoplastic left heart syndrome (HLHS) rate, *Canada (excluding Québec),* 1998–2009*

Year	Total births**	Number of cases	Prevalence rate (95% CI) per 10,000 total births
1998	269,079	88	3.3 (2.6–4.0)
1999	265,746	78	2.9 (2.3–3.7)
2000	258,667	92	3.6 (2.9–4.4)
2001	263,350	90	3.4 (2.7–4.2)
2002	259,505	68	2.6 (2.0–3.3)
2003	264,981	62	2.3 (1.8–3.0)
2004	266,277	75	2.8 (2.2–3.5)
2005	269,530	74	2.7 (2.2–3.4)
2006	275,737	54	2.0 (1.5–2.6)
2007	286,098	76	2.7 (2.1–3.3)
2008	290,725	74	2.5 (2.0–3.2)
2009	292,312	70	2.4 (1.9–3.0)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2009.
*Québec was excluded because data were not available for all years. **Total births include live births and stillbirths. CI—Confidence Interval

TABLE B4.2F

Common ventricle (CV) defect rate, *Canada (excluding Québec),* 1998–2009*

Year	Total births**	Number of cases	Prevalence rate (95% CI) per 10,000 total births
1998	269,079	30	1.1 (0.8–1.6)
1999	265,746	33	1.2 (0.9–1.7)
2000	258,667	34	1.3 (0.9–1.8)
2001	263,350	16	0.6 (0.3–1.0)
2002	259,505	22	0.8 (0.5–1.3)
2003	264,981	14	0.5 (0.3–0.9)
2004	266,277	12	0.5 (0.2–0.8)
2005	269,530	11	0.4 (0.2–0.7)
2006	275,737	18	0.7 (0.4–1.0)
2007	286,098	18	0.6 (0.4–1.0)
2008	290,725	21	0.7 (0.4–1.1)
2009	292,312	16	0.5 (0.3–0.9)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2009.
*Québec was excluded because data were not available for all years. **Total births include live births and stillbirths. CI—Confidence Interval

TABLE B4.3A/B

Congenital heart defect (CHD) rate, by province/territory, *Canada (excluding Québec),* 2000–2009 combined*

Province/territory	Total births**	Number of cases	Prevalence rate (95% CI) per 10,000 total births
Newfoundland and Labrador	46,294	704	152.1 (141.0–163.7)
Prince Edward Island	14,039	142	101.2 (85.2–119.2)
Nova Scotia	88,046	743	84.4 (78.4–90.7)
New Brunswick	70,791	678	95.8 (88.7–103.3)
Ontario	1,368,360	13,530	98.9 (97.2–100.6)
Manitoba	143,598	1,242	86.5 (81.7–91.4)
Saskatchewan	124,584	1,133	90.9 (85.7–96.4)
Alberta	430,089	4,752	110.5 (107.4–113.7)
British Columbia	409,270	3,225	78.8 (76.1–81.6)
Yukon	3,912	45	115.0 (83.9–153.9)
Northwest Territories	6,984	76	108.8 (85.7–136.2)
Nunavut	5,529	130	235.1 (196.4–279.2)
CANADA‡	2,727,182	26,668	97.8 (96.6–99.0)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 2000–2009.
*Québec was excluded because data were not available for all years.
**Total births include live births and stillbirths.
‡Includes data for unknown provinces/territories. CI—Confidence Interval

TABLE B5.1

Total orofacial clefts (OFCs) and cleft palate (CP) rates, *Canada, 1998–2007*

Year	Total births*	Orofacial clefts (OFCs)		Cleft palate (CP)	
		Number of cases	Prevalence rate (95% CI) per 10,000 total births	Number of cases	Prevalence rate (95% CI) per 10,000 total births
1998	343,823	617	17.9 (16.6–19.4)	250	7.3 (6.4–8.2)
1999	338,407	628	18.6 (17.1–20.1)	272	8.0 (7.1–9.1)
2000	330,398	564	17.1 (15.7–18.5)	223	6.7 (5.9–7.7)
2001	336,835	544	16.2 (14.8–17.6)	229	6.8 (5.9–7.7)
2002	331,527	547	16.5 (15.1–17.9)	241	7.3 (6.4–8.2)
2003	338,417	511	15.1 (13.8–16.5)	234	6.9 (6.1–7.9)
2004	339,687	553	16.3 (15.0–17.7)	232	6.8 (6.0–7.8)
2005	347,476	565	16.3 (14.9–17.7)	260	7.5 (6.6–8.4)
2006	359,618	511	14.2 (13.0–15.5)	227	6.3 (5.5–7.2)
2007	372,724	559	15.0 (13.8–16.3)	247	6.6 (5.8–7.5)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1998–2007.
*Total births include live births and stillbirths. CI—Confidence Interval

TABLE B5.1A

Cleft lip (CL) and cleft lip with or without cleft palate (CL±CP) rates, *Canada, 1998–2007*

Year	Total births*	Cleft lip (CL)		(CL±CP)	
		Number of cases	Prevalence rate (95% CI) per 10,000 total births	Number of cases	Prevalence rate (95% CI) per 10,000 total births
1998	343,823	98	2.9 (2.3–3.5)	367	10.7 (9.6–11.8)
1999	338,407	97	2.9 (2.3–3.5)	356	10.5 (9.5–11.7)
2000	330,398	114	3.5 (2.8 –4.1)	341	10.3 (9.3–11.5)
2001	336,835	102	3.0 (2.5–3.7)	315	9.4 (8.3–10.4)
2002	331,527	103	3.1 (2.5–3.8)	310	9.4 (8.3–10.5)
2003	338,417	91	2.7 (2.2–3.3)	280	8.3 (7.3–9.3)
2004	339,687	102	3.0 (2.4–3.6)	323	9.5 (8.5–10.6)
2005	347,476	101	2.9 (2.4–3.5)	309	8.9 (7.9–9.9)
2006	359,618	103	2.9 (2.3–3.5)	294	8.2 (7.3–9.2)
2007	372,724	118	3.2 (2.6–3.8)	322	8.6 (7.7–9.6)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1998–2007.
*Total births include live births and stillbirths. CI—Confidence Interval

TABLE B5.2A/B

Orofacial cleft (OFC) rate, by province/territory, *Canada, 1998–2007 combined*

Province/territory	Total births*	Number of cases	Prevalence rate (95% CI) per 10,000 total births
Newfoundland and Labrador	46,644	93	19.9 (16.1–24.4)
Prince Edward Island	14,078	21	14.9 (9.2–22.8)
Nova Scotia	89,344	177	19.8 (17.0–23.0)
New Brunswick	72,161	102	14.1 (11.5–17.2)
Québec	748,444	1,092	14.6 (13.7–15.5)
Ontario	1,354,028	1,978	14.6 (14.0–15.6)
Manitoba	141,087	293	20.8 (18.5–23.3)
Saskatchewan	122,222	273	22.3 (19.8–25.1)
Alberta	416,281	712	17.1 (15.9–18.4)
British Columbia	406,580	809	19.9 (18.5–25.3)
Yukon	3,938	§	§
Northwest Territories	7,434	13	17.5 (9.3–29.9)
Nunavut	4,186	16	38.2 (21.8–62.1)
CANADA‡	3,438,912	5,599	16.3 (15.9–16.7)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1998–2007.
*Total births include live births and stillbirths. §Rate suppressed due to small cell counts (<5).
‡Includes data for unknown provinces/territories. CI—Confidence Interval

TABLE B6.1

Limb deficiency defect (LDD) rate, *Canada, 1998–2007*

Year	Total births*	Number of cases	Prevalence rate (95% CI) per 10,000 total births
1998	343,823	156	4.5 (3.9–5.3)
1999	338,407	127	3.8 (3.1–4.5)
2000	330,398	123	3.7 (3.1–4.4)
2001	336,835	138	4.1 (3.4–4.8)
2002	331,527	137	4.1 (3.5–4.9)
2003	338,417	127	3.8 (3.1–4.5)
2004	339,687	119	3.5 (2.9–4.2)
2005	347,476	129	3.7 (3.1–4.4)
2006	359,618	117	3.3 (2.7–3.9)
2007	372,724	129	3.5 (2.9–4.1)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1998–2007.
*Total births include live births and stillbirths. CI—Confidence Interval

TABLE B6.2A/B

Limb deficiency defect (LDD) rate, by province/territory, *Canada, 1998–2007 combined*

Province/territory	Total births*	Number of cases	Prevalence rate (95% CI) per 10,000 total births
Newfoundland and Labrador	46,644	16	3.4 (2.0–5.6)
Prince Edward Island	14,078	§	§
Nova Scotia	89,344	29	3.3 (2.2–4.7)
New Brunswick	72,161	18	2.5 (1.5–3.9)
Québec	748,444	354	4.7 (4.2-5.2)
Ontario	1,354,028	401	3.0 (2.7–3.3)
Manitoba	141,087	62	4.4 (3.4–5.6)
Saskatchewan	122,222	63	5.2 (4.0–6.6)
Alberta	416,281	202	4.9 (4.2–5.6)
British Columbia	406,580	147	3.6 (3.1–4.2)
Yukon	3,938	§	§
Northwest Territories	7,434	§	§
Nunavut	4,186	§	§
CANADA‡	3,438,912	1,302	3.8 (3.6–4.0)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1998–2007.
*Total births include live births and stillbirths. ‡Includes data for unknown provinces/territories.
§Rate suppressed due to small cell counts (<5). CI—Confidence Interval

TABLE B7.1

Gastroschisis rate, *Canada, 2002–2009**

Year	Total births**	Number of cases	Prevalence rate (95% CI) per 10,000 total births
2002	236,492	73	3.1 (2.4–3.9)
2003	241,824	72	3.0 (2.3–3.7)
2004	251,727	87	3.5 (2.8–4.3)
2005	267,658	95	3.5 (2.9–4.3)
2006	356,541	130	3.6 (3.0–4.3)
2007	369,701	139	3.8 (3.2–4.4)
2008	289,172	128	4.4 (3.7–5.3)
2009	290,664	129	4.4 (3.7–5.3)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 2002–2009.
*Some provincial data were only available for certain years: New Brunswick (2004–2009), Québec (2006–2007) and Manitoba (2005–2009). All others were available for the full period (2002–2009)
**Total births include live births and stillbirths. CI—Confidence Interval

TABLE B7.2A/B

Gastroschisis rate, by province/territory, *Canada, 2002–2009 combined**

Province/territory	Total births**	Number of cases	Prevalence rate (95% CI) per 10,000 total births
Newfoundland and Labrador	36807	15	4.1 (2.3–6.7)
Prince Edward Island	11244	9	8.0 (3.7–15.2)
Nova Scotia	69993	40	5.7 (4.1–7.8)
New Brunswick	41999	15	3.6 (2.0–5.9)
Québec	167104	27	1.6 (1.1–2.4)
Ontario	1103527	307	2.8 (2.5–3.1)
Manitoba	74502	53	7.1 (5.3–9.3)
Saskatchewan	100331	46	4.6 (3.4–6.1)
Alberta	355671	182	5.1 (4.4–5.9)
British Columbia	329083	143	4.3 (3.7–5.1)
Yukon	2819	§	§
Northwest Territories	5600	§	§
Nunavut	5099	10	19.6 (9.4–36.1)
CANADA‡	2,303,779	853	3.7 (3.5–4.0)

Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 2002–2009.
*Combined rate for the eight-year period 2002–2009, with the exception of New Brunswick 2004–2009, Manitoba 2005–2009 and Québec 2006–2007
**Total births include live births and stillbirths. §Rate suppressed due to small cell counts (<5).
‡Includes data for unknown provinces/territories. CI—Confidence Interval