Neural Tube Defects in Australia, 2007–2011:

Before and after implementation of the mandatory folic acid fortification standard

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Never Stand Still | Medicine | National Perinatal Epidemiology & Statistics Unit

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Glossary

Aboriginal and/or Torres Strait Islander
A person who identifies themselves and is accepted by their community as a descendant of the first peoples of Australia or the Torres Strait Islands. Health data require only self-identification. Also referred to as Indigenous.

Acephaly
A congenital condition in which the entire head is absent.

Anencephaly
A type of neural tube defect that involves most of the brain and upper part of the skull. See Table 1 for the full definition.

Baby
A fetus or an infant.

Birth
The complete expulsion from the uterus of a live born or stillborn baby of at least 20 weeks gestational age or weighing 400 g or more.

Conception
The commencement of a pregnancy.

Congenital condition
A condition in a fetus or a baby that arises during gestation. This is the preferred term in this report that is synonymous with 'congenital anomaly', 'developmental anomaly' and 'birth defect'.

Craniorachischisis
A neural tube defect in which bones of the skull and spine do not fuse and parts of the brain and spinal cord are exposed.

Encephalocoele
A type of neural tube defect affecting one part of the brain and skull. See Table 1 for the full definition.

Estimated date of conception
The calculated date when gestation commenced, expressed as a month and year.

Fetus
Pregnancy tissues that grow and develop into a baby.

Gestation
The period of pregnancy during which a baby develops, commencing with conception and ending with birth, miscarriage or termination of pregnancy.

Herniation
Protrusion of an organ through the wall of the cavity in which it is normally situated.

Infant
A child ages less than one year.

Iniencephaly
A type of neural tube defect affecting the occipital bones at the back of the head, the spinal bones of the neck region and underlying brain and spinal cord tissues.

Meninges
Tissue layer covering the brain and spinal cord.

Meningocoele
A type of spina bifida in which a cyst protrudes comprised of meninges.

Meningomyelocoele
A type of spina bifida in which a cyst protrudes comprised of meninges and tissues of the spinal cord.

Myelocoele
A type of spina bifida in which a cyst protrudes from the spine comprised of tissues of the spinal cord.

Neural tube defects
A group of congenital conditions that comprises anencephaly, spina bifida and encephalocoele.

Occurrence of NTD
The first time a woman has a baby with a neural tube defect.

Periconceptional period
Unspecified period of time from immediately before to immediately after conception. For the purpose of NTD prevention with folates this period spans 4 weeks before and 4 weeks after conception.

Rachischisis
A type of neural tube defect in which several bones of the spine do not fuse and the spinal cord is exposed.

Recurrence of NTD
A baby with neural tube defect for a woman who has had a baby with a neural tube defect in a previous pregnancy.

Spina bifida
Neural tube defect that involves the spinal cord and the spine. See Table 1 for the full definition.

List of Abbreviations

µg	microgram
ACHI	Australian Classification of Health Interventions
AIHW	Australian Institute of Health and Welfare
An	anencephaly
APD	admitted patient data
BDR	Birth Defects Register
CI	confidence interval
CR	congenital anomaly register
En	encephalocoele
FSANZ	Food Standards Australia New Zealand
g	gram
ICBDSR	International Clearinghouse for Birth Defects Surveillance and Research
ICD9-BPA	International Statistical Classification of Diseases and Related Health Problems, 9th Revision, British Paediatric Association modification
ICD10-AM	International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian modification
na	Not applicable
nc	Not calculated
NSW	New South Wales
np	Not presented
NT	Northern Territory
NTD	Neural tube defects
PDC	perinatal data collection
PDR	perinatal death review
Qld	Queensland
QAPDC-CAD	Congenital anomaly data component of the Queensland Admitted Patient Data Collection
NND	neonatal death
NNS	neonatal survivors
NCCH	National Centre For Classification in Health
NPDC	National Perinatal Data Collection
RBD	registrations of births and deaths
RoCC	Register of Congenital Conditions
RR	relative rate
SA	South Australia
SABDR	South Australian Birth Defects Register
SB	stillbirth
SB-T	Stillbirth and termination of pregnancy
SBf	Spina bifida
TOP	termination of pregnancy
Vic	Victoria
VR	vital (birth and death) registration
WA	Western Australia
WARDA	Western Australia Register of Developmental Anomalies

Executive summary

Background

The mandatory folic acid fortification standard was introduced in Australia in September 2009. The main purpose was to increase folate consumption among women of reproductive age in the whole population, as women who become pregnant require sufficient amounts of this vitamin during the first weeks of pregnancy to prevent neural tube defects (NTD). The addition of 200–300 µg of folic acid per 100 g of flour to all wheat flour used for making bread was expected to reduce the rate of NTD by between 4% and 16%.

The purpose of this report is to compare the NTD rate in Australia before and after the mandatory folic acid fortification standard came into effect.

Methods

The NTD rate is the number of babies with NTD among pregnancies that ended in a birth or a termination of pregnancy for congenital anomaly in a defined population divided by the number of total births (live births and stillbirths) in that population. Birth prevalence of NTD is the proportion of all babies born in a defined population who have NTD.

NTDs were categorised as isolated NTD if there were either no co-existing congenital anomalies or only co-existing anomalies that occur as a consequence of NTD. Isolated NTD have been considered to be more strongly associated with folate insufficiency.

Information about 1,030 babies with NTD from pregnancies that ended in 2007 to 2011 was obtained from health authorities in New South Wales, Queensland, Western Australia, South Australia, the Northern Territory and Tasmania. The Victorian Birth Defects Registry had not been updated to cover all of these years and the Australian Capital Territory was not able to provide data.

NTD rates in 2007-2011 were used to assess NTD ascertainment by states and territories. These ranged from 14.3 per 10,000 births in South Australia to 5.1 per 10,000 births in Tasmania. Babies with NTD may be lost from, or added to, jurisdictional ascertainment if women travel interstate for birth or termination of pregnancy. This may contribute to the very low ascertainment of NTD in Tasmania, where no NTD were found from pregnancies terminated before 20 weeks gestation. NTD rates of 7.0 NTD per 10,000 births in New South Wales in 2007-2011 were half (51.4%) of those in the states considered to have near complete ascertainment. This is considered to result from difference in the methods used to find NTD affected babies. Relative ascertainment in New South Wales in the current study period was similar to that in 2004-2008 (51.2%) and in 1999-2003 (53.4%). Although data collection methods varied between jurisdictions, they were consistent over the study period within each jurisdiction. Data values to assign populations for comparison over time were missing from Tasmania (18.8%), the Northern Territory (5.3%) and New South Wales (2.1%). These NTD rates compared populations defined in time by the year in which the pregnancy ended and in place by the state in which the birth or pregnancy termination occurred and used denominator data from annual reports of the National Perinatal Data Collection (NPDC).

Jurisdictional data for residents of New South Wales, Queensland, Western Australia, South Australia and the Northern Territory were used to determine NTD rates for the study. Results from the population omitting New South Wales residents were undertaken as a sensitivity analysis. Including data from New South Wales with substantial under-ascertainment will result in lower absolute NTD rates, but as long as the level of under-ascertainment is constant over time this does not affect the proportional difference between rates from different time periods.

NTD rates before and after introduction of the mandatory fortification standard were compared in population groups defined in time by their date of conception and in place by the maternal state of residence. Babies conceived in the baseline period from October 2006 to December 2008 were compared with babies conceived in the standard period from October 2009 to March 2011. The transition period from January to September 2009 allowed for phased implementation of the mandatory folic acid standard. Denominators for these rates were obtained from customised tabulations of unpublished birth data for residents of participating states and territories provided by the Australian Institute of Health and Welfare (AIHW) from the National Perinatal Data Collection (NPDC).

NTD rates before and after introduction of the mandatory folic acid standard

There was a statistically significant fall of 14.4% (95%CI 0.7, 26.2) NTD per 10,000 conceptions in the standard period relative to the NTD rates in the baseline period among residents of New South Wales, Queensland, Western Australia, South Australia and the Northern Territory. Omitting New South Wales residents, there was a non-significant 12.5% (95%CI -4.7, 28.9) fall in the rate of NTD per 10,000 conceptions across the same periods for residents of Queensland, Western Australia, South Australia and the Northern Territory. NTD rates in the latter population are the best available absolute estimates of NTD rates, which fell from 12.8 per 10,000 conceptions (95%CI 11.4,14.3) in the baseline period to 11.2 NTD per 10,000 conceptions (95%CI 9.7, 12.8) in the standard period.

Isolated NTD rates declined progressively among conceptions in the three study periods that resulted in a birth, whereas rates of non-isolated NTD did not. The 14.8% (95%CI -0.3, 27.7) reduction in isolated NTD rates in the total study population and the 13.8% (95%CI -5.1, 29.2) in the population omitting New South Wales residents were of the same order of magnitude as for reductions in overall NTD rates. A degree of misclassification of isolated and non-isolated NTD is likely because detection of co-existing anomalies varies according to the duration of pregnancy. More rigorous and systematic investigation at source may be required to improve the quality of information needed to properly distinguish isolated and non-isolated NTD.

The study found reductions in NTD rates over time for babies of teenagers and babies of Aboriginal or Torres Strait Islander women. Neither of these groups of women had benefited from earlier strategies to increase periconceptional folate intake and reduce NTD such as health education, folic acid supplementation and voluntary fortification of foods implemented prior to mandatory fortification.

Maternal age

The rate of NTD affected babies of teenage mothers from Queensland, Western Australia, South Australia and the Northern Territory was 18.6 per 10,000 conceptions in the baseline period that ended as a birth and 7.0 per 10,000 conceptions in the standard period that ended as a birth, representing a statistically significant fall of 62.6% (95%CI 9.1, 86.7). The relative differences in NTD rates over time were statistically non-significant for other maternal age groups. The falls became progressively smaller with increasing maternal age up to the age group 30-34 years. For babies of mothers aged 20-24, 25-29, and 30-34 years the NTD rate per 10,000 conceptions in the standard period relative to the baseline period fell by 24.6%, 17.2% and 14.4% respectively. NTD rates rose by 32.6% in the standard period relative to the baseline period among babies with mothers aged 35 or older. There were no NTD-affected babies missing data for maternal age in this population compared with 59 (6.6%) in the total study population. When residents of New South Wales were included there was a statistically significant 54.8% fall in NTD rates per 10,000 conceptions over time among babies with teenage mothers, reducing levels of fall in NTD rates that were not statistically significant as maternal age increased and reversal in the direction of change to a 19.2% increase in NTD rates per 10,000 conceptions in the standard period relative to that in the baseline period for babies of the oldest mothers. When NTD were restricted to isolated NTD, the strong inverse association with maternal age in the baseline period disappeared in the standard period.

Aboriginal and Torres Strait Islander mothers

In the population omitting New South Wales there was a statistically significant 80.2% (95%CI 49.1, 92.8) reduction in NTD rates between the baseline and standard periods among babies with mothers of Aboriginal or Torres Strait Islander origin. The NTD rate fell from 22.8 NTD-affected babies per 10,000 conceptions in the baseline period that ended as a birth to 4.5 NTD affected babies per 10,000 conceptions in the standard period that ended as a birth. A large, statistically significant reduction (74.2% 95%CI 45.1, 87.9) was also seen among babies of Aboriginal or Torres Strait Islander mothers in the study population including New South Wales residents. The falls in NTD rates between the baseline and standard periods among babies of non-Indigenous mothers were statistically non-significant both in the population omitting New South Wales (4.4%) and in the total study population (9.1%). There were 5 (0.8%) NTD-affected babies missing data for Indigenous status from the population omitting New South Wales compared with 38 (4.2%) in the total study population.

Change in NTD birth prevalence

NTD birth prevalence in 2011 following introduction of the mandatory folic acid standard was10.9% (95%CI -11.8, 29.0) lower than in 2007–2008 (5.5 versus 4.9 per 10,000 total births respectively) in New South Wales, Queensland, Western Australia, South Australia, Tasmania and the Northern Territory. The reduced birth prevalence does not appear to have resulted from an increased uptake of pregnancy termination.

Conclusions

This study found reductions in NTD rates for babies conceived in the period after introduction of the mandatory folic acid standard relative to the baseline period for the total study population comprising residents of New South Wales, Queensland, Western Australia, South Australia and the Northern Territory and the population omitting residents of New South Wales. The 14.4% (significant) and 12.5% (non-significant) reductions in NTD rates in these populations, respectively, are in keeping with those predicted for the level of folic acid fortification introduced.

These results need to be considered in the context of the short study period post-fortification for which data were available and the relative rarity of NTD both of which contribute to variability in NTD rates. Ongoing monitoring of Australian NTD rates are required to confirm whether these reductions will be sustained.

This study does not prove that mandatory folic acid fortification of a staple food caused the reduction of NTD. These results need to be viewed in the context of other studies that measure the effects of mandatory folic acid fortification in individuals and information about the extent and reach of ongoing voluntary folic acid fortification of foods within the target population. Importantly, substantial falls in the NTD rate among women who had been missed by earlier strategies to increase periconceptional folate intake suggest that a more equitable and whole population reduction in NTD has been achieved.

Background

Neural tube defects

Neural tube defects (NTD) are a group of congenital conditions consisting of anencephaly, spina bifida and encephalocoele. The neural tube normally closes by the end of the fourth week after conception and develops into the central nervous system (brain and spinal cord). Failure of any part of the neural tube to close results in a neural tube defect, characterised by localised disorganisation of the central nervous system and abnormal development of the adjacent bones and other tissues.

NTD are associated with high rates of pregnancy loss and perinatal mortality. Surviving children often need neonatal intensive care, surgery and rehabilitation and may have lifelong and serious health issues and require specialised care. This has impacts on education and the capacity to participate in society and in the workforce. Prevention of NTD is therefore a priority for families, health services and governments.

Causes of neural tube defects

Folate insufficiency

The most widely known cause of NTD is insufficient folate during the first weeks of pregnancy. Folate deficiency was first suggested as a contributor to NTD 50 years ago (Hibbard et al. 1965) and tested in a series of observational studies over the next two decades.

The role of folate as a key nutrient for prevention of NTD was confirmed in two large randomised controlled trials that compared various combinations of vitamin supplements given to women who were planning pregnancy. The Medical Research Council Vitamin Study Research Group found women with NTD diagnosed in a previous pregnancy who were given preparations containing folic acid had a 72% lower incidence of NTD in a subsequent pregnancy compared with those who were given preparations without folic acid (Wald and Sneddon 1991). The Hungarian Family Planning Program trial randomised non-pregnant women with no history of an NTD-affected pregnancy to receive either a trace element and multivitamin supplement containing folic acid or a supplement of trace elements alone (Czeizel and Dudás 1992). No NTD were found among women who received the supplement containing folic acid, compared with the expected rate of NTD in the group who did not receive folic acid.

Further evidence for the preventative effect of folic acid came from the evaluation of a large-scale public health campaign in northern China that provided folic acid supplements to women preparing for marriage. The rate of NTD among fetuses or infants of compliant women decreased by between 40% to 85% compared with pre-supplementation rates (Berry et al. 1999).

The NTD protective effect of peri-conception supplementation with folic acid against both first-time occurrence and recurrence of NTDs has been summarised by meta-analyses of trials of periconceptional folic acid supplementation (De-Regil et al. 2010). This review found that between 50–70% of NTD could be prevented by maternal ingestion of folic acid before and during early pregnancy.

Other causes

Several recent reviews have discussed other factors that contribute to the development of NTD (Detrait et al. 2005, Padmanabhan 2006, Osterhues et al. 2012, Finnell et al. 2013, Wallingford et al. 2013). In addition to folates, other nutrients such as vitamin B12, choline and zinc may also have a role in the development of NTD. NTD may be caused by exposures to organic solvents, pesticides or

medications. Poor periconceptional glycaemic control has been associated with NTD in the offspring of diabetic women, and may also contribute to the excess NTD among obese women. In vitro fertilisation and maternal hyperthermia have also been implicated. These risk factors explain a minority of NTD cases (Botto et al. 1999, Osterhues et al. 2012).

The small (2–5%) increased risk of NTD recurrence following an affected pregnancy and some familial clustering of NTD suggest a heritable component, but no Mendelian, or single-gene pattern (Padmanabhan 2006). A small minority of NTD occur as part of a syndrome or single-gene mutation or as a result of chromosomal abnormalities, specifically extra copies of chromosome (trisomy) 13 or 18 and various other chromosome rearrangements (Detrait et al. 2005, Chen 2008).

In addition to NTD that arise as part of a chromosomal abnormality or genetic syndrome, NTD can be present together with other major congenital anomalies. These two groups have been distinguished from NTD that appear in isolation (Khoury et al. 1982, Dolk et al. 1991). Non-isolated NTD and isolated NTD are considered to originate from different causes, and are excluded or reported separately in recent studies on NTD prevalence (Mosley et al. 2009, Parker et al. 2014).

Cellular processes of neural tube formation are complex (Padmanabhan 2006, Wallingford et al. 2013), and while progress has been made in understanding the process of neural tube closure, the underlying mechanisms that drive these changes are still not fully understood (Osterhues et al. 2012). As a consequence, causal pathways that link the actions of folates and the other known risk factors to NTD closure are yet to be determined.

Prevention of neural tube defects with folic acid

Folic acid

Folic acid is a stable, synthetic form of folate, which is a naturally occurring B group vitamin. Folate is not stored in the body, so regular consumption is needed to ensure that sufficient levels are available. The critical period for NTD prevention is the 4 weeks before and after conception and the target population are women of reproductive age, and more particularly those who become pregnant.

Strategies before mandatory fortification

A variety of strategies have been employed to increase folate consumption among women of reproductive age, including targeted health education, dietary advice, provision of folic acid supplements and voluntary fortification of foods.

In Australia, the National Health and Medical Research Council (NHMRC) issued a statement on the relationship between dietary folic acid and NTD in 1992 that was updated in 1993(NHMRC 1994). This recommended:

- provision of dietary advice to all women planning or likely to become pregnant to increase intake of folate rich foods
- periconceptional folic acid supplements for all women planning a pregnancy
- specific measures for women with a higher risk of having an NTD-affected baby because of prior birth of an NTD affected-baby; a family history of NTD; or use of anticonvulsant drugs
- folic acid fortification of staple foods, such as bread and cereals
- health education for health professionals and the public
- ongoing monitoring of NTD rates and the folate intake.

The range of activities based on the NHMRC statement in Western Australia, South Australia and Victoria have been summarised (Bower and Halliday 2013). The campaigns were successful overall in reducing NTD. However, women who were young, unmarried, or having their first baby, were less

likely to be aware of the folate health promotion message and less likely to take folic acid supplements periconceptionally (Bower et al. 2005). Also, there was no decline in NTD for Indigenous women, for whom higher rates of NTD continued at more or less the same level, while the already lower NTD rates among babies of non-Indigenous women declined (Bower et al. 2004).

A review of public health programs to promote increased periconceptional intake of folates and programs to promote and provide folic acid supplements found these strategies to be expensive, their effects time-limited, and to have missed many women, particularly those not amenable to health education and those whose pregnancies were unplanned (Molloy 2005). In Australia, as elsewhere, folic acid supplementation uptake did not increase above 40% of the target population (Bower and Stanley 2004).

Folic acid fortification of foods was first implemented in Australia in 1995, and in the years that followed, the number and range of foods that could be fortified increased. There was no comprehensive data to determine the extent and reach of voluntarily fortified food products in the Australian population, so it was not easy to assess their impact (Bower and Stanley 2004).

Evaluation of the voluntary folic acid fortification program was carried out in 2001 (Abraham and Webb 2001). This found firstly that the effectiveness criterion of 70% of women consuming more than 400 µg of folate per day set by the NHMRC Expert Panel on Folate Fortification had not been met. Secondly, and most importantly, that participation by the food industry had been low, despite some evidence that the market share of breads and breakfast cereals was quite high.

Mandatory fortification

Mandatory fortification of a staple food was first put into practice in the United States in 1998, and soon after by Canada and other countries. The success of international mandatory fortification with folic acid (Honein et al. 2001, De Wals et al. 2003) combined with the limitations of changes to diet, supplementation and voluntary fortification paved the way for mandatory fortification of food with folic acid in Australia.

In 2004, Food Standards Australia New Zealand (FSANZ) convened the Folate Scientific Advisory Group, comprised of clinicians and public health nutritionists with expertise in epidemiology and/or folate nutrition to develop the mandatory folic acid fortification standard. This group comprehensively assessed the potential benefits and risks of increasing folic acid intake within the population (FSANZ 2006). They concluded that the main purpose of fortification of a staple foodstuff is to increase folate consumption among women aged 16 to 44 years in the whole population so that those who conceive have more of this vitamin available at the critical stage of development of the central nervous system during the first weeks of life to prevent NTD.

The recommended standard required the addition of 200–300 µg of folic acid per 100g of flour to all wheat flour used for making bread, with the exception of organic bread.

A model to predict the relationship between increased folic acid intake, increased serum folate and a decreased risk of NTD (Wald et al. 2001) was applied to the increased intake predicted from the introduction of the mandatory fortification standard in Australia. Among 300–350 annual pregnancies the number affected by NTD would be expected to fall by between 14 and 49 cases (FSANZ 2006), representing a decrease in the incidence of NTD in the range of 4% to 16%.

The mandatory folic acid fortification standard was introduced in Australia from 13 September 2009.

NTD rate in Australia before 2009

Health promotion, supplementation and voluntary fortification instituted in the 1990s reduced the rate of NTD. Between 1992 and 2005, a 32.7% fall in NTD rates from 18.0 per 10,000 births to 13.3 per 10,000 births was observed in the three Australian states, Victoria, South Australia and Western Australia (Abeywardana and Sullivan 2008). This mirrored findings in individual jurisdictions over the same period (Halliday and Riley 2000, Chan et al. 2001, Bower et al. 2002).

The NTD rates in Victoria, South Australia and Western Australia fell further from 12.7 per 10,000 births in 2006 to 12.1 per 10,000 births in 2007 to an all-time low of 10.7 per 10,000 births in 2008 (Macaldowie and Hilder 2011). The average annual decline in the rate of NTD between 1998 and 2008 averaged 0.2 per 10,000 births and was more evident for spina bifida, with no appreciable change in the occurrence of either anencephaly or encephalocoele. Higher rates of NTD were reported among babies of teenagers and women aged 35 years or older; among babies of women living in areas of relative disadvantage; among women living in remote areas; and among women of Aboriginal or Torres Strait Islander origin.

In Queensland, researchers identified data for pregnancies that ended in a termination for congenital anomaly before 20 weeks gestation in the Queensland Health Admitted Patient Data Collection from 2007 onwards (Howell 2009). When combined with birth data from the Queensland Birth Defects Register, there were 73 NTD-affected pregnancies in 2007–08 and 76 in 2008–09 of which 52.1% and 51.3% were from termination of pregnancy for each year respectively (QHHSC 2011). There were 60,683 babies born in Queensland in 2007–08 and 62,232 in 2008–09 (Laws and Sullivan 2009, Laws et al. 2010, Laws et al. 2011), yielding an NTD rate of 12.1 per 10,000 births in 2007–08 and 12.2 per 10,000 births in 2008–09. These NTD rates were similar to those from Victoria, Western Australia and South Australia and in the calendar years 2007 and 2008 (Macaldowie and Hilder 2011).

Purpose of the report

The purpose of this report is to compare the rate of NTD in Australia among babies conceived before and after the introduction of the mandatory folic acid fortification standard in September 2009.

Methods

Definitions

NTD-affected baby

A fetus or infant diagnosed as having a neural tube defect.

Neural tube defect

Anencephaly, spina bifida or encephalocoele are described in Table 1, which lists the ICD-10, and ICD-9-BPA classifications for the diseases included for each condition.

NTD rate

NTD rate is the number of NTD-affected babies from a birth or termination of pregnancy for congenital anomaly regardless of pregnancy gestation divided by the number of total babies born (live births and stillbirths) in a specified time and place.

The definition for calculating the NTD rate is that defined by the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR 2010) as the standard frequency measure of congenital

anomaly occurrence. The NTD rate will therefore be comparable with measures reported by other studies of NTD in Australia and elsewhere that apply the same definition.

Table 1: Definition of types of neural tube defects

Types of NTD	Description[(a)]	ICD10[(b)]	ICD9-BPA[(c)]
Anencephaly:	Total or partial absence of the cranial vault, the covering skin, and the brain missing or reduced to a small mass. Includes craniorachischisis and iniencephaly but excludes acephaly.	Q00.0–Q00.2	740.00–740.29
Spina bifida:	Herniation or exposure of the spinal cord and/or meninges through an incompletely closed spine. Includes meningocoele, meningomyelocoele, myelocoele, and rachischisis. Excludes spina bifida occulta, saacrococcygeal teratoma without dysraphism.	Q05.0–Q05.9	741.00–741.99
Encephalocoele:	Herniation of the brain and/or meninges through a defect in the skull.	Q01.0–Q01.2, Q01.8, Q01.9	742.00–742.09

Notes

(a) Descriptions use definitions of the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR 2010).

(b) International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD10) is used to code deaths. The Australian modification (ICD10-AM) codes are applied in Queensland to congenital anomalies from the Queensland Perinatal Data Collection and the Queensland Hospital Admitted Patient Data Collection.

(c) International Statistical Classification of Diseases and Related Health Problems, 9th Revision, British Paediatric Association modification (BPA 1979) codes are used in jurisdictional congenital anomaly registers in New South Wales, Western Australia and South Australia

NTD birth prevalence

The NTD birth prevalence is the number of NTD-affected individuals among all births (live births and stillbirths) divided by the number of total babies born (live births and stillbirths) in a specified time and place. Births include termination of pregnancy after 20 weeks gestation.

Isolated NTD

NTD that have either no co-existing congenital anomalies or only have co-existing anomalies directly related to the NTD.

Non-isolated NTD

NTD with co-existing congenital anomalies that are not directly related to the NTD.

Populations in person, place and time

Pregnancy populations were defined in person by the babies that result from the pregnancies in accordance with the standard definitions of congenital anomaly rates.

The pregnancy population defined in time by the start of gestation (date of conception) and place by maternal state/territory of usual residence, were used to calculate NTD rates per 10,000 conceptions that resulted in a birth in specified time periods before and after the introduction of the mandatory folic acid fortification standard.

Pregnancy population defined in time by the end of gestation (birth, or termination of pregnancy) and in place by the state/territory in which the birth (or termination of pregnancy) occurred, were used to calculate annual NTD rates per 10,000 births in specified jurisdictions.

Study data

Data on cases of neural tube defects were sought from health authorities in each state or territory. New South Wales, Queensland, Western Australia, South Australia, Tasmania and the Northern

Territory agreed to provide data. Data from the Victorian Congenital Anomalies Register (formally the Victorian Birth Defects Register) were not available for the whole study period. The Australian Capital Territory did not have a congenital anomaly data collection.

A standardised request for NTD data (Appendix C) was provided to all source data custodians who agreed to provide data. This defined key data items, including the calculation of estimated date of conception and value domains for grouped data items to facilitate the extraction of comparable data from each jurisdiction. Estimated date of conception was derived by source data providers using the most precise data available.

The NTD data provided for this study are summarised in Table 2. Data from New South Wales, Western Australia and South Australia were sourced from congenital anomaly registers, which include information about congenital anomalies from multiple sources about pregnancies that ended in a birth, as well as pregnancies that ended in a termination of pregnancy before 20 weeks gestational age.

Queensland provided two data extracts: NTD among births notified to the Queensland Perinatal Data Collection (QPDC) and NTD in the table of fetal congenital anomaly diagnoses related to the Queensland Hospital Admitted Patient Data Collection (QHAPDC-CAD). The former include NTD from pregnancies of 20 or more weeks of gestational age and the latter from pregnancies that ended before 20 weeks gestation. QHAPDC-CAD have been accumulating data since July 2007 (Howell 2009).

In the Northern Territory and Tasmania, NTD cases were sought from multiple routinely collected jurisdictional data sources: perinatal data collections (PDCs); admitted patient data (APD); perinatal death review (PDR) data; and vital (birth and death) registration data (VR). Records were manually reconciled to collate records for the same pregnancy.

Table 2: Source of NTD data from each state or territory

State/Territory	Prepared as:	Source data [(a)]	Reference period[(b)]
New South Wales	Extract	CR	Jan 2007 to Dec 2011
Queensland	Extracts	PDC QHAPDC-CAD	Jan 2007 to Dec 2011 Jul 2007 to Dec 2011
Western Australia	Extract	WARDA	Jan 2007 to Dec 2011
South Australia	Extract	SABDR	Jan 2007 to Dec 2011
Northern Territory	Collated data	PDC/APD/PDR /VR	Jan 2007 to Dec 2011
Tasmania	Collated data	PDC/PDR	Jan 2007 to Dec 2012

Notes

(a) Source data: CR=congenital anomalies register; PDC = perinatal data collection; APD = admitted patient or hospital inpatient data; PDR = perinatal death review data; BDR = birth defects register; VR = vital (birth and death) registrations RD = research data; QHAPDC-CAD is the congenital anomaly data component of the Queensland Hospital Admitted Patient Data Collection. WARDA is the Western Australian Register of Developmental Anomalies; SADBR is the South Australian Birth Defects Register.

(b) The reference periods for data collections are based on date on which the pregnancy ended.

Further information about each of the data collections is provided in Appendix A.

Institutional, jurisdictional and Aboriginal ethics committee approval for the study was granted to obtain data for this study. Details of the committees are given in Appendix B.

Study periods

The mandatory folic acid fortification standard was introduced into Australia in September 2009. This had been widely publicised and some flour mills may have commenced fortification before this date. Three time periods were therefore selected for this study and applied to conceptions: a 'baseline' period before mandatory fortification commenced until the end of December 2008; a 'transition' period

from January 2009 to the end of September 2009; and a 'standard' period from the beginning of October 2009 to the end of March 2011, during which the fortification standard was mandated.

Conceptions were counted in the baseline period from October 2006 to December 2008 for New South Wales, the Northern Territory, South Australia and Western Australia, and from April 2007 to December 2008 for Queensland. The later start of the baseline period in Queensland reflects the later availability of complete NTD data (Table 2).

The commencement of the baseline period and end of the standard period were informed by the reported duration of NTD-affected pregnancies which ranged from 10 weeks to 42 weeks (Appendix D). Limits were set so that pregnancies of all durations had an equal chance of being counted in each period to avoid potential bias. The shortest pregnancy duration set the limit for the commencement of the baseline period three months before the start of the reference period for all source data collections. Commencement at earlier dates would miss NTD-affected pregnancies with shorter gestations. For example, a pregnancy conceived in September 2006 that continued for 12 weeks would not be expected to appear in data collections of pregnancies that ended in 2007. Conversely, the longest pregnancy duration set the end point for the standard period.

Categorising isolated and non-isolated NTD

Non-NTD conditions present in babies along with NTD were categorised as 'related to NTD' if the condition arose as a result of the presence of the NTD. If the non-NTD condition arose separately from another cause it was categorised as 'unrelated to NTD'. Co-existing conditions where the causes are not well understood, or comprise several conditions with differential relationships to NTD were categorised as 'uncertain relationship to NTD'.

An existing schema categorising co-existing conditions according to the relationship with the NTD (Macaldowie and Hilder 2011) was extended to cover all non-NTD conditions present among the NTD affected babies in this study (see Appendix G). Conditions not included in the previous report or ambiguously grouped were reviewed by two experts, one of whom had advised on the schema for the earlier report. The conditions listed for each category reflect the conditions present in study babies and are not exhaustive.

NTD were classified as 'isolated' if there were no unrelated conditions present and as 'non-isolated' if there was one or more unrelated conditions present. Related conditions could co-exist with either isolated or non-isolated NTD. If conditions with an uncertain relationship to NTD were present with unrelated conditions, the NTD were also classified as 'non-isolated'. However, if these were the only other conditions present or were present with related conditions, the NTD were classified as 'uncertain'. Appendix G Table G9 summarises these criteria for classifying NTD as 'isolated', 'non-isolated' and 'uncertain'.

Data processing and statistical analysis

Records identified as out of scope were flagged and censored, standard formats were applied and data were combined into a single dataset. NTD data from each of the participating jurisdictions were examined for completeness, data quality and consistency with study definitions.

Assessment of data quality

The number of records from each jurisdiction with missing data values was determined. Complete ascertainment of NTD requires that data are available about NTD-affected babies from pregnancies that ended before 20 weeks gestational age. South Australia and Western Australia are considered to have near complete ascertainment of NTD. Both these states benefit from statutory collection of data about termination of pregnancy for congenital anomaly. Assuming that NTD rates in these

jurisdictions applied elsewhere during the study period provided a rudimentary assessment of the expected number NTD-affected babies.

Analysis

Data processing and analysis were performed using Statistical Analysis Software (SAS) version 9.3. NTD rates and birth prevalence rates were calculated by combining tabulations of NTD study data and tabulated denominator data that applied the same person, place and time definitions.

Standard descriptive statistics (Armitage et al. 2002) were calculated: (1)proportional rate difference (%diff) is the difference between the NTD rate in the baseline period and the NTD rate in the standard period as a proportion of the NTD rate in the baseline period, expressed as a percentage; and (2) relative rate (RR) is the NTD rate in the standard period relative to (divided by) the NTD rate in the baseline period (the reference period) together with 95% confidence intervals for the relative rates.

RRs are standard epidemiological measures of effect. RRs below unity indicate a protective effect and those above unity indicate increased risk of disease. The RR is statistically significant if the 95% confidence limits do not cross unity. The width of the interval indicates the precision of the measure, reflecting population size and disease frequency. The proportional rate difference and relative rate are reciprocal (%diff=(RR-1)*100). Positive values for proportional rate differences indicate increased risk and negative values indicate decreased risk. Similar transformations can be applied to obtain the upper and lower confidence limits for proportional risk difference from those for RR, if required. Upper and lower confidence intervals are presented to 3 decimal places in the tables to assist this process.

In view of New South Wales under-ascertainment and level of missing values in the data obtained for NTD babies (Appendix D). A sensitivity analysis was undertaken whereby NSW data were omitted from calculation of NTD rates to assess possible bias from missing data that could skew the results of comparisons over time.

A secondary benefit of this analysis is that NTD rates omitting NSW are better measures of the absolute risk of NTD in Australia during this period.

Results

Information about 1,030 babies with NTD from pregnancies ending in a birth or a termination of pregnancy for congenital abnormality between 2007 and 2011 from New South Wales, the Northern Territory, Queensland, Western Australia, South Australia, and Tasmania were available for the study.

Classification of NTD

In total there were 400 babies with anencephaly, 525 babies with spina bifida and 119 babies with encephalocoele (Table 3). A hierarchical classification was applied when multiple NTD conditions were present in the same baby. This assigns anencephaly over spina bifida or encephalocoele, and spina bifida over encephalocoele (Table 3) and is used throughout the remainder of the report.

Table 3: NTD individual conditions and groups

	Type of NTD classification[(a)]			Total[(b)]	
	Anencephaly	Spina bifida	Encephalocoele	Babies	Conditions
NTD conditions		***Number***			
Anencephaly				400	400
and no other NTD	387				
with spina bifida	10				
with encephalocoele	3				
Spina bifida				515	525
and no other NTD		514			
with encephalocoele		1			
Encephalocoele				115	119
and no other NTD			115		
Total NTD	**400**	**515**	**115**	**1,030**	**1,044**

Notes

(a) This is a hierarchical system that allocates each baby to one NTD group. Anencephaly takes precedence over all other NTD conditions, and spina bifida takes precedence over encephalocoele.

(b) A baby can have more than one condition, and the total number of conditions therefore exceeds the total number of babies.

Jurisdictional data quality

Jurisdictional NTD rates for populations defined by the state or territory and year of birth or termination of pregnancy (TOP) across the whole study period (2007-2011) were higher in South Australia (14.3 per 10,000 births) and Western Australia (13.1 per 10,000 births) than in other jurisdictions (Table 4). These states have congenital anomaly registers that employ active case finding and benefit from statutory collection of termination of pregnancy (TOP) data (Grayson et al. 2005). Ascertainment of NTD is considered to be near complete in these states.

The lowest jurisdictional NTD rate of 5.1 per 10,000 births in 2007-2011 was found in Tasmania which was a quarter (26.3%) of the number expected (Table 4). Cases were obtained exclusively from birth and perinatal death data collections. No NTD were found from TOP before 20 weeks gestation. The study predates decriminalisation of TOP in Tasmania in 2013. NTD rates in the Northern Territory were 9.8 per 10,000 births in 2007-2011. In addition to the 19 NTD- affected babies found among births and terminations of pregnancy in the territory there were 5 NTD occurrences for residents of the Northern Territory in other jurisdictions. Queensland rate of 10.7 NTD-affected babies per 10,000 births was 78.7% of that expected if the rates in South Australia and Western Australia in the study period prevailed (Table 4). Babies with NTD may be lost from, or added to jurisdictional ascertainment, if women travel interstate to birth or for TOP. South Australia health services are routinely used by residents of the Northern Territory and western New South Wales. NTD-affected babies would have been lost to the study if from participating jurisdictions women travelled to Victoria for TOP.

New South Wales has a congenital anomalies register that includes data from TOPs and births. However, NTD ascertainment for this register relies on a passive system of notifications from health service providers. NTD rates of 7.0 NTD per 10,000 births in New South Wales in 2007-2011 were half (51.4%) those in the states considered to have near complete ascertainment. Relative ascertainment in New South Wales in the current study period was similar to that in 2004-2008 (51.2%) and 1999-2003 (53.4%). Although data collection methods varied between jurisdictions, they were consistent over the study period within each jurisdiction.

Data values to assign populations for comparison over time were substantially missing from Tasmania (18.8%), and to a lesser extent from the Northern Territory (5.3%) and New South Wales (2.1%).

Table 4: NTD data quality by state and territory of record origin

	WA	SA	NT	Qld[(b)]	NSW	Tas	Total
NTD-affected babies	204	143	19	311	337	16	1,030
NTD rate 2007-2011[(a)(b)]	13.1	14.3	9.8	10.7	7.0	5.1	
% of expected cases [(b)]	n.a.	n.a.	72.2	78.7	51.4	26.3	n.a.
%TOP[(c)]	53.9	60.1	47.4	42.1	31.2	..	42.8
Incomplete data values (%)							
Study period	..	..	5.3	..	2.1	18.8	1.6
Maternal Indigenous status	1.0	..	..	1.3	13.1	100.0	6.4
Maternal age	..	..	..	..	23.1	..	7.6

Notes

(a) NTD rates per 10,000 births in populations defined by state or territory of birth or termination of pregnancy (TOP) in 2007-2011. Denominators from birth data published in *Australia's mothers and babies* series

(b) The NTD-affected babies from TOP were not available in Queensland before July 2007 (Table3). NTD rates were calculated from July 2007 to December 2011 omitting 14 NTD-affected babies and births from January to July 2007.

(c) Proportion of expected cases is the number of observed cases as proportion of the number of cases expected if rates of NTD in the states with near complete ascertainment (South Australia and Western Australia), applied in each jurisdiction. The proportions are expressed as a percentage (%) of expected cases.

(d) Termination of pregnancy before 20 weeks gestational age.

n.a not applicable

.. null result

Study populations

There were 894 babies with NTD who were conceived during one of the three study periods by women resident in the total study population comprising New South Wales, Queensland, Western Australia, South Australia and the Northern Territory, whose data were used to determine NTD rates.

The 17 NTD-affected babies of Tasmanian residents were excluded along with 6 NTD babies of women who were Australian non-residents, residents of a non-participating jurisdiction or missing residence status (Appendix D Tables D5). A further 39 study babies with NTD conceived before the start of the baseline period and 74 conceived after the end of the standard period did not contribute to NTD rates for conceptions in study periods.

NTD birth prevalence was determined for resident populations from all participating jurisdictions.

NTD rates among babies conceived in the study periods

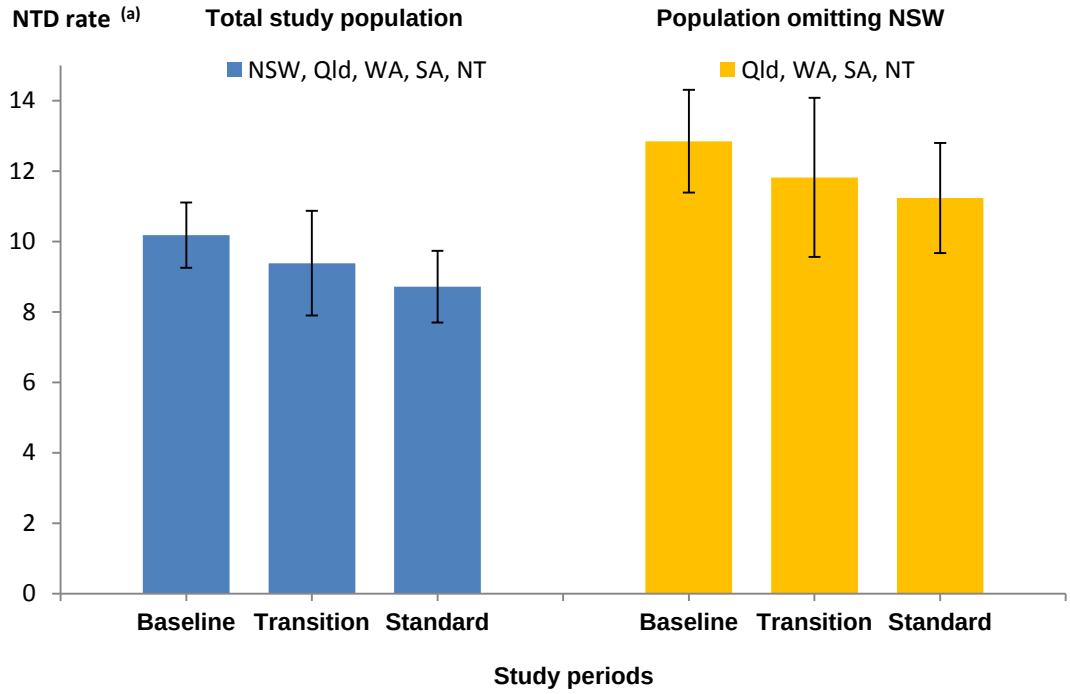
Among the total study population, comprising residents of New South Wales, Queensland, Western Australia, South Australia and the Northern Territory there were 459 babies with NTD who were conceived during the baseline period; 153 babies with NTD who were conceived during the transition period; and 282 babies with NTD who were conceived during the standard period.

When the 294 (32.9%) NTD-affected babies resident in New South Wales were omitted from the total study population, the number of babies conceived in the baseline, transition and standard periods were respectively 297, 105 and 198.

The NTD rates per 10,000 conceptions declined progressively across the three study periods in the total study population (residents of New South Wales, Queensland, Western Australia, South Australia) and the population omitting New South Wales residents (Figure 1).

The rates omitting New South Wales are better absolute measures of NTD risk, but have wider confidence intervals.

Figure 1: NTD rates among conceptions in the three study periods



Notes:

Error bars represent 95% confidence intervals for NTD rates

(a) NTD per 10,000 conceptions that resulted in a birth.

For every 10,000 conceptions in the total study population that resulted in a live birth or a stillbirth the NTD rates (95%CI) in the baseline, transition and standard periods respectively were 10.2 (9.3, 11.1), 9.4 (7.9, 10.9) and 8.7 (7.7, 9.7) per 10,000 conceptions that resulted in a birth. NTD rates (95% confidence intervals) for the population omitting NSW residents were 12.8 (11.4, 14.3), 11.8 (9.6, 14.1) and 11.2 (9.7, 12.8) per 10,000 conceptions respectively in the baseline, transition and standard periods that resulted in a birth.

The NTD relative rate (RR) for residents of New South Wales, Queensland, Western Australia, South Australia and the Northern Territory was 0.86 and the relative rate 95% confidence interval (RR 95%CI) ranged from 0.74 to 0.99. This represents a statistically significant protective effect for conception in the standard period compared with conception in the baseline period. Alternatively this can be expressed as a statistically significant fall in the NTD rate from the baseline period to the standard period of 14.4% with a 95% confidence interval for this fall ranging from 0.7% to 26.2%. The 12.5% (95%CI -4.7, 28.9) fall in the NTD rate in the standard period relative to the baseline period in the population omitting residents of New South Wales was of a similar order to that for the total study population, but did not reach statistical significance.

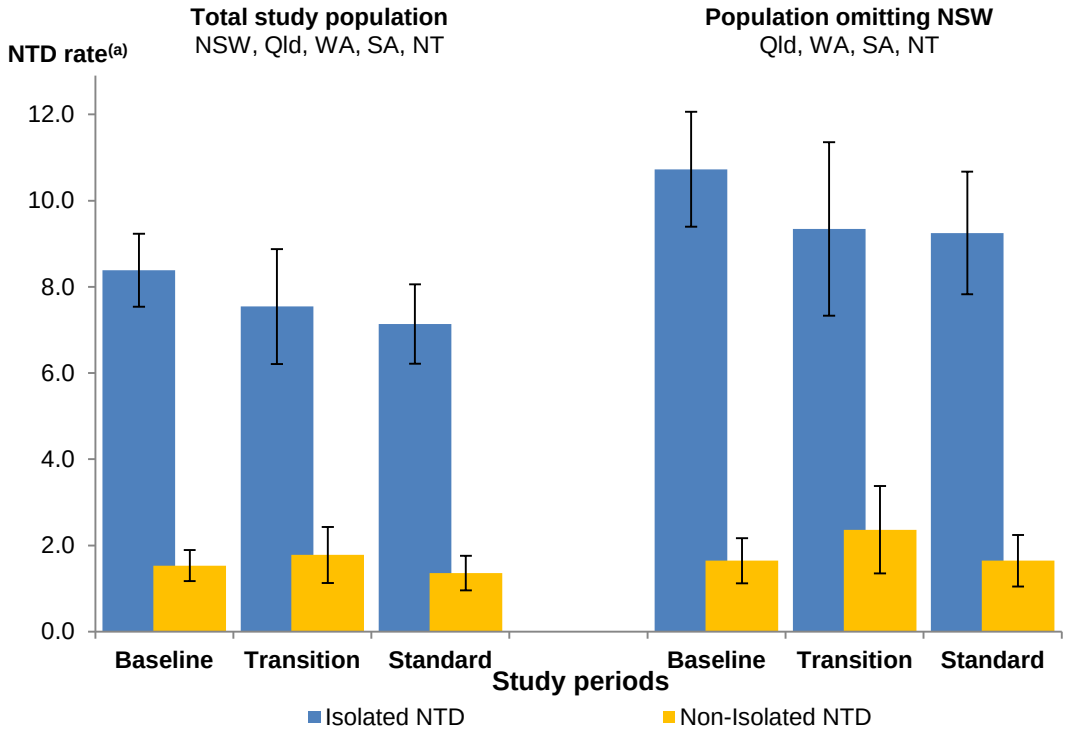
NTD rates by isolated and non-isolated NTD

Isolated NTD were differentiated from non-isolated NTD because they have been considered to be more closely associated with folate insufficiency than with other causes of NTD. The proportion of NTD-affected babies with isolated NTD in the total study population and the population omitting NSW were respectively 81.9% and 82.3% (Appendix tables F2 and G2). Further results describing characteristics of babies with isolated and non-isolated NTD are available in Appendix E.

Figure 2 shows the isolated NTD and non-isolated NTD together with the 95% confidence intervals around the rates. In both populations, isolated NTD rates declined progressively across the three study periods while rates among non-isolated NTD rates first increased between the baseline and the transition period, and then decreased in the standard period. The 14.8% (95%CI -0.3, 27.7) decline in the isolated NTD rate in the total study population, and 13.8% (95%CI -5.1, 29.2) decline in isolated NTD in the population omitting New South Wales were similar to the declines in overall NTD rates in these two populations.

Isolated NTD results may be subject to misclassification. The proportion of NTD classified as non-isolated varied by pregnancy outcome, with half as many non-isolated NTD found among pregnancies terminated before 20 weeks gestational age (Appendix table E6). This may reflect different standards of pathological investigation and reporting of non-NTD anomalies among pregnancies that ended in a termination of pregnancy and those that ended in a birth. The proportion of NTD classified as non-isolated each year varied, but not systematically (Appendix table E6).

Figure 2: Isolated and non-isolated NTD rates in the three study periods



Notes:

Error bars represent 95% confidence intervals for NTD rates

(a) NTD rate per 10,000 conceptions that resulted in a birth.

NTD rate by NTD type

Changes over time in the rates of anencephaly, spina bifida and encephalocoele were assessed for babies conceived in the three study periods to residents of Queensland, Western Australia, South Australia and the Northern Territory. The population omitting New South Wales was used because of the substantially lower ascertainment of anencephaly relative to spina bifida observed in this state (Appendix Table D4).

Anencephaly rates fell from 6.2 per 10,000 conceptions in the baseline period that resulted in a birth to 4.6 per 10,000 conceptions in the transition period that resulted in a birth, and then rose to 5.4 per 10,000 conceptions in the standard period that resulted in a birth. Spina bifida rates rose from 5.3per

10,000 conceptions in the baseline period that resulted in a birth to 6.2 per 10,000 conceptions in the transition period that resulted in a birth and then fell to 5.0 per 10,000 conceptions in the standard period that resulted in a birth. Encephalocoele rates declined progressively with rates in the baseline, transition and standard periods respectively of 1.3, 1.1 and 0.9 per 10,000 conceptions respectively in each period that ended as a birth.

NTD rates for all three types of NTD were lower in the standard period than in the baseline period, but none of these differences were statistically significant (Appendix table G1).There was a 13.5% reduction in the rate of anencephaly, a 6.2% reduction in the rate of spina bifida and a 34.4% reduction in the rate of encephalocoele between the baseline and standard periods. Rates of encephalocoele are based on substantially smaller numbers than other NTD types and are subject to greater random variation.

NTD rates by maternal age

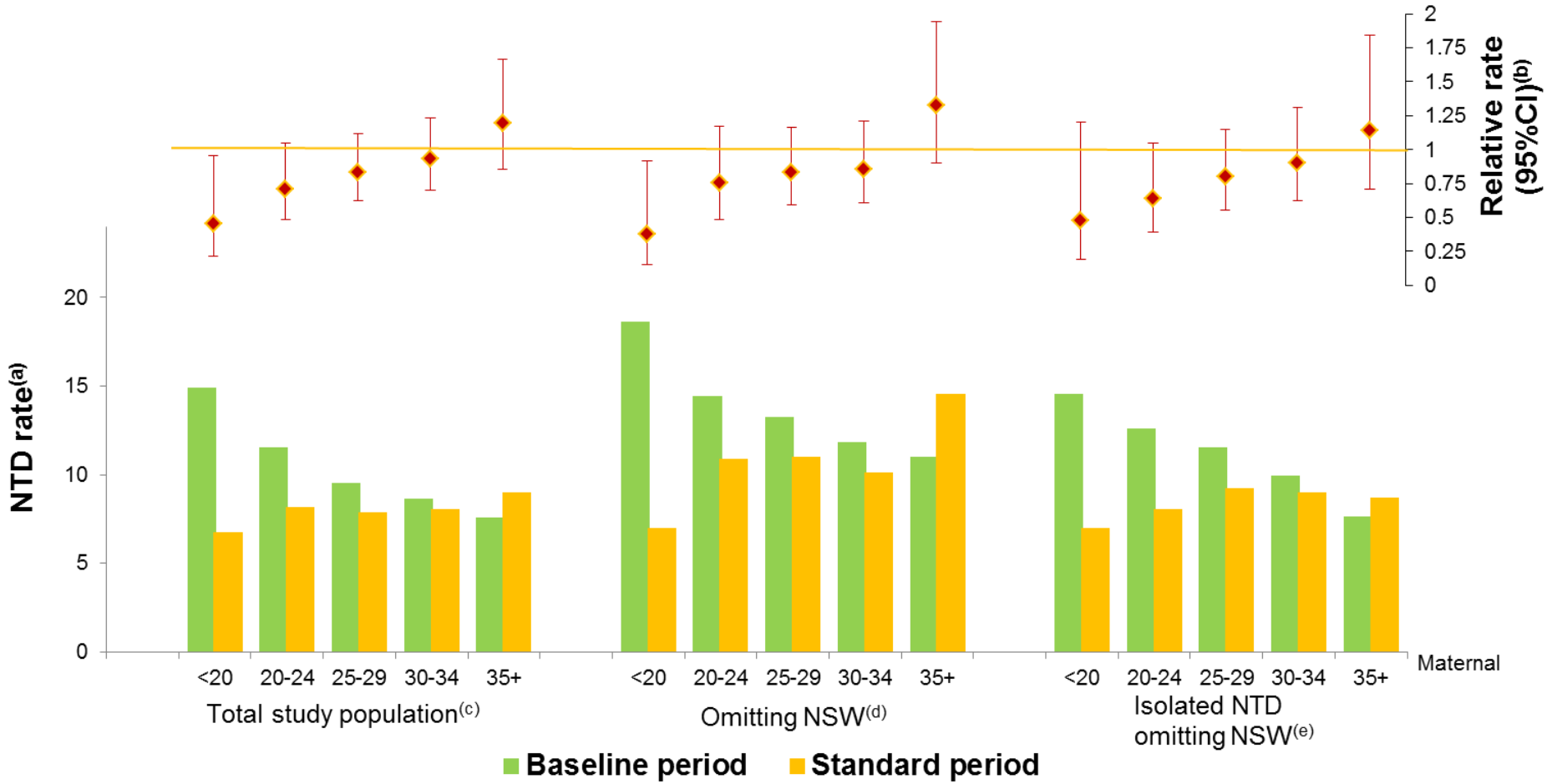
Babies of teenage mothers resident in New South Wales, Queensland, Western Australia, South Australia and the Northern Territory showed a statistically significant 54.8% (95%CI 4.8%, 78.5%) reduction in the rate of NTD per 10,000 conceptions the standard period that resulted in a birth relative to conceptions in the baseline period that resulted in a birth (Figure 3, Appendix Table F3). Among babies of teenage mothers resident in Queensland, Western Australia, South Australia and the Northern Territory the 62.6% decline in the NTD rate per 10,000 conceptions was also statistically significant (95%CI 8.1%, 84.7%) (Figure3, Appendix Table G2).

The level of the protection was progressively lower, but not statistically significant for older maternal age groups (Figure 3) in both populations. For babies of mothers aged 20-24, 25-29, and 30-34 years the NTD rate per 10,000 conceptions in the standard period relative to the baseline period fell by 28.8%, 16.9% and 6.8% respectively for the total study population (Appendix Table F3) and 24.6%, 17.2% and 14.4% respectively in the population omitting New South Wales (Appendix Table G5). The NTD rate rose in the standard period relative to the baseline period by 19.2% for mothers aged 35 or older in the total study population and 32.6% for such mothers in the population omitting New South Wales.

Maternal age-stratified results for the total study population did not include 59 NTD-affected babies with missing data for maternal age. None of the NTD-affected babies in the population omitting New South Wales were missing data for maternal age.

Isolated NTD rates for the population omitting NSW stratified by maternal age are also included in Figure 3. Isolated NTD are considered to be more closely associated with folate insufficiency. There is strong inverse association of the rate of isolated NTD with maternal age for babies conceived in the baseline period which manifests as a gradient of decreasing rates of NTD with advancing maternal age. This relationship almost disappears for babies conceived in the standard period, where the rates of isolated NTD per 10,000 conceptions are relatively stable for babies with mothers aged 25 or older. Furthermore, increasing NTD rates in the standard period particularly in the oldest maternal age group can be attributed to non-isolated NTD. Changes in the rates of isolated NTD rates between the baseline period and the standard period followed the same pattern as for all NTD.

Figure 3: NTD rates, and NTD relative rates among conceptions, by maternal age



Notes

(a) NTD (isolated NTD) rate per 10,000 conceptions that resulted in a birth.
(b) Relative rate is the NTD (isolated NTD) rate in the standard period relative to the NTD (Isolated NTD) rate in the baseline period.
(c) 'Total study' population is for residents of NSW, Qld, WA, SA and NT – refer to Appendix Table F3.
(d) The population 'Omitting NSW' is for residents Qld, WA, SA and NT. This sensitivity analysis was undertaken to assess potential effects of missing data – refer to Appendix Table G3.
(e) The 'Isolated NTD' group are considered more sensitive to the inadequate dietary folate – refer to Appendix Table G5.

NTD rate by maternal Indigenous status

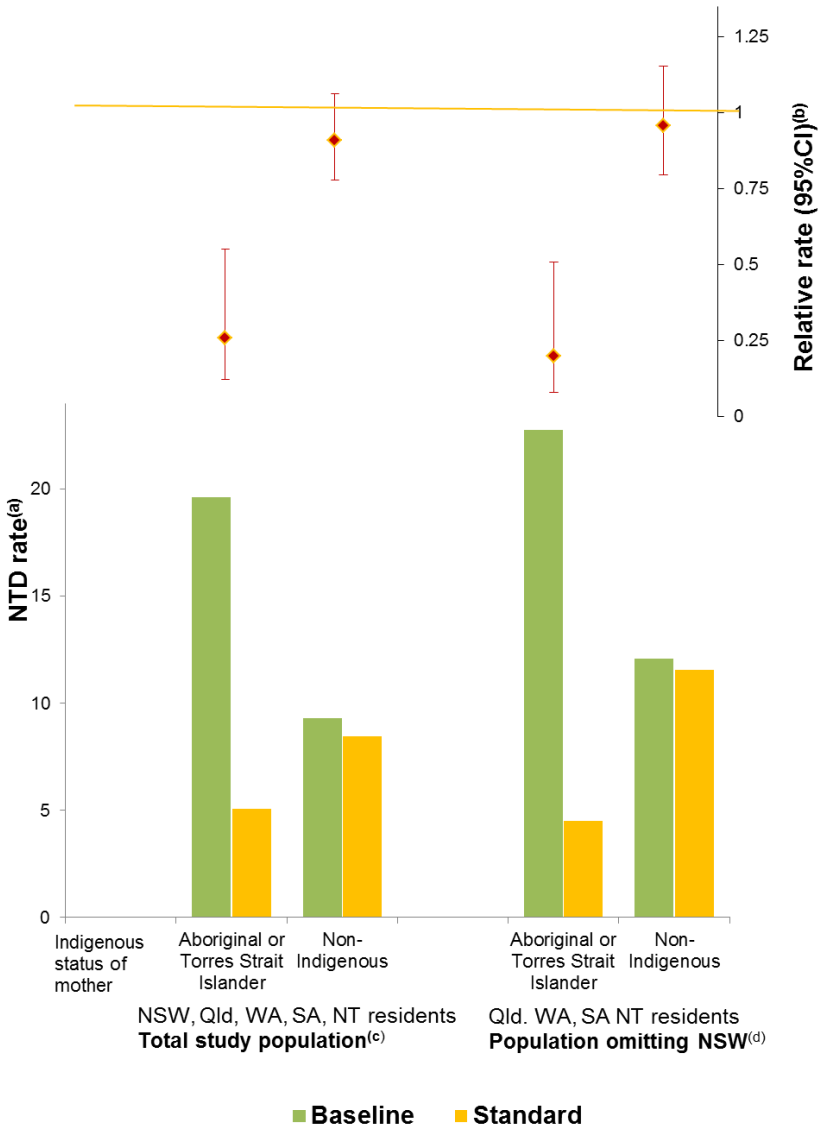
The NTD rates for babies with mothers of Aboriginal or Torres Strait Islander origin resident in New South Wales, Queensland, Western Australia, South Australia and the Northern Territory had an NTD rate 19.6 per 10,000 conceptions conceived in the baseline period that resulted in a birth, which was twice the rate of conceptions in the same period among babies of non-Indigenous mothers (9.3 per 10,000 conceptions that resulted in a birth). Among the population omitting New South Wales in the baseline period for babies with mothers of Aboriginal or Torres Strait Islander origin, the NTD rate (22.8 per 10,000 conceptions that resulted in a birth) was less than twice that among conceptions of mothers of non-Indigenous origin (12.8 per 10,000 conceptions that resulted in a birth).

The NTD rates for babies conceived in the standard period by mothers of Aboriginal or Torres Strait Islander origin were substantially lower both in the total study population (5.1 per 10,000 conceptions that resulted in a birth) and the population omitting New South Wales (4.5 per 10,00 conceptions that resulted in a birth) than in the baseline period. In both populations these NTD rates were lower than those among babies conceived by non-Indigenous mothers, which were respectively 8.5 and 11.6 per 10,000 conceptions that resulted in a birth.

Figure 4 also shows that the relative rates of NTD per 10,000 conceptions between the baseline and the standard periods were protective for babies with mothers of Aboriginal or Torres Strait Islander origin in the total study population (RR 0.26 RR95%CI 0.12, 0.55) and in the population omitting New South Wales (RR 0.20 RR95%CI 0.08, 0.51). Expressed as the percentage difference relative to the baseline period NTD rates among babies with mothers of Aboriginal or Torres Strait Islander origin fell by 74.2% (95%CI 0.7, 87.7) in the total study population and by 80.2% (95%CI 49.2, 93.2) in the population omitting New South Wales. There were more modest and statistically non-significant falls in NTD rates for babies of non-Indigenous mothers estimated as 9.1% in the total study population (Table F2 and Figure 4) and 4.4% in the population omitting New South Wales (Table F4 and Figure 4).

In total there were 48 babies with teenager mothers among the 894 NTD-affected babies in the total study population conceived in one of the three study periods (Table F3). Of these, 8 (16.7%) were teenage mothers of Aboriginal or Torres Strait Islander origin, which is of the same order as in the birth population as a whole (Laws and Sullivan 2009, Li et al. 2013). Thus, despite the largest reductions in NTD rates over the three study periods seen for any population sub-group, mothers of Aboriginal or Torres Strait Islander origin could not account for most of the fall in NTD rates among teenagers. Nor did teenage mothers account for the fall in NTD among babies with mothers of Aboriginal or Torres Strait Islander origin .In all three analyses, the effect of maternal Indigenous status is reversed in the standard period compared with the effect in the baseline period.

Figure 4: NTD rates and NTD relative rates among conceptions by maternal Indigenous status



Notes

(a) NTD rate per 10,000 conceptions that resulted in a birth.
(b) Relative rate is the NTD rate in the standard period relative to the NTD rate in the baseline period.
(c) 'Total study' population is all informative conceptions in the study – refer to Table F4.
(d) The group 'Omitting NSW' are presented as a sensitivity analysis to assess potential effects of missing data – refer to Table G3.

NTD rates among annual births

Table 5 presents the annual rates of NTD per 10,000 births by the state or territory of birth or pregnancy termination.

The number of NTD babies in Queensland in 2007 was incomplete because the research data (from which details of NTD babies from pregnancies that ended as a termination before 20 weeks gestation were sourced), only commenced in July 2007. The 14 NTD babies born in Queensland before July 2007 were omitted from the calculation of annual rates. Data were combined for 2007–2008 and 2010–2011 for the Northern Territory because of the small number of NTD babies born each year. The NTD rates in the Northern Territory, even for the combined years, are based on small numbers and prone to random variation.

Table 5: NTD rates by state and year of birth

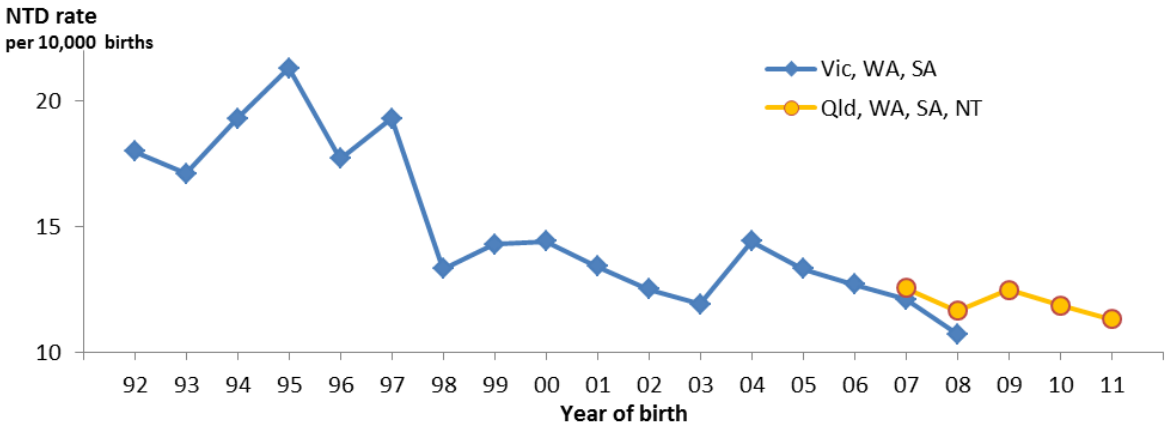
Year of birth	State of birth[a] NSW	Qld[b]	WA	SA	NT[c]	NSW, Qld, WA, SA, NT	Qld, WA, SA, NT
				NTD			
2007	75	44	37	22	[6	387	240
2008	72	63	44	24			
2009	73	63	41	37	[8	433	289
2010	71	65	36	39			
2011	46	62	46	21	5	180	134
				Total births[d]			
2007	96,016	30,100	30,074	19,751	[7,641	391,961	199,609
2008	96,336	61,400	30,674	19,969			
2009	96,434	62,048	31,219	19,898	[7,796	427,172	234,252
2010	96,486	62,025	31,265	20,001			
2011	97,238	62,166	32,204	20,344	3,927	215,879	118,641
				NTD rate[e]			
2007	7.8	14.6	12.3	11.1	[7.9	9.9	12.0
2008	7.5	10.3	14.3	12.0			
2009	7.6	10.2	13.1	18.6	[7.7	10.1	12.3
2010	7.4	10.5	11.5	19.5			
2011	4.7	10.0	14.3	10.3	12.7	8.3	11.3

Notes

(a) State of birth is the same as state of pregnancy termination for NTD babies.
(b) Data for Queensland NTD were incomplete before July 2007 (see Table 2). The 14 NTD births in January to June 2007 were omitted for consistency.
(c) Northern Territory results were combined for 2007–2008 and 2009–2010 because of small numbers of NTD.
(d) Total births comprise annual births and the derived number of births in Queensland from July to December 2007. These include both unmodified material from, and modified material based on Australian Institute of Health and Welfare; and the University of New South Wales material published in 'Australia's mothers and babies' reports for the years 2007 to 2011 (Laws et al, 2009, Laws et al 2010, Laws et al 2011, Li et al 2012, Li et al, 2013), **Source data for these reports:** Australian Institute of Health and Welfare (AIHW) National Perinatal Data Collection. Details of the collection retrieved 25 February 2016 from http://www.aihw.gov.au/mothers-and-babies/
(e) NTD rate per 10,000 births.

Figure 5 shows the annual NTD rates per 10,000 births between 2007 and 2011 in Queensland, Western Australia, South Australia and the Northern Territory from the present study as a separate, overlapping series with NTD rates per 10,000 births in Victoria, Western Australia and South Australia in 1991 to 2008 (Abeywardana and Sullivan 2008, Macaldowie and Hilder 2011). These results are presented to contextualise the data from the current study with those reported previously. These two series represent different populations and are not directly comparable.

Figure 5: Trends in NTD rates by year of birth, 1992 to 2011



Annual rates of pregnancy termination before 20 weeks gestation

Over the five years from 2007 to 2011 at least 44.6% of NTD babies were diagnosed with NTD before 20 weeks gestation. The majority of these are babies with anencephaly which is recognised as a lethal condition. The proportion of babies with NTD whose gestation ended with a termination of pregnancy before 20 weeks gestation has not changed substantially between 2007–2008 and 2011 (Table 6).

Table 6: NTD from a termination of pregnancy, by year of pregnancy end

Year of birth	NTD TOP[(a)]	NTD[(b)]	TOP rate
	Number		*Per cent*
2007– 08[(b)]	169	387	43.7
2009–10	200	433	46.2
2011	77	180	42.8
2007–11	446	1,000	44.6

Notes

(a) NTD termination of pregnancy (TOP) before 20 weeks gestation.
(b) Data for Queensland NTD babies were incomplete before July 2007 (see Table 3). The 14 NTD births in January to June 2007 have not been included.

Birth prevalence

The numbers of NTD babies born from 2007 to 2011 in New South Wales, Queensland, Western Australia, South Australia, Tasmania and the Northern Territory are shown in Table 7 by year of birth, state of birth and type of NTD. NTD births were further divided into stillbirths, neonatal deaths (that is, babies born alive who died in the first 28 days), and those who survived the neonatal period.

The birth prevalence of NTD in Table 7 ranges from 4.8 per 10,000 births in New South Wales to 5.9 per 10,000 births in Queensland.

The annual birth prevalence of NTD was 4.9 per 10,000 births in 2011 and 5.5 per 10,000 births in 2007–2008. This represents a 10.9% (95%CI -11.8, 29.0) reduction in the NTD birth prevalence in the year after introduction of the mandatory folic acid fortification standard relative to the two years prior to introduction of the standard. This does not appear to have been the result of increased rates of pregnancy termination before 20 weeks gestation (Table 6).

Table 7: NTD birth, NTD birth prevalence by year of birth, state of birth and NTD classification

	Total births[(a)]	NTD babies[(b)]				
		SB	NND	NNS	Total	Birth prevalence[(c)]
			Number			
Year of birth						
2007	216,472	50	26	44	120	5.6 (4.6, 6.5)
2008	218,851	57	21	41	119	5.4 (4.5, 6.4)
2009	218,367	66	12	44	122	5.6 (4.6, 6.6)
2010	218,416	63	14	38	115	5.2 (4.3, 6.2)
2011	220,747	55	18	35	108	4.9 (4.0, 5.8)
State of birth						
NSW	482,681	91	41	99	231	4.8 (4.2, 5.4)
Qld	306,274	100	36	44	180	5.9 (5.0, 6.7)
WA	154,298	53	6	31	90	5.8 (4.6, 7.0)
SA	99,134	33	4	20	57	5.7 (4.3, 7.2)
NT	19,073	n.p.	n.p.	n.p.	10	5.2 (2.0, 8.5)
Tas	31,393	n.p.	n.p.	n.p.	16	5.1 (2.6, 7.6)
NTD classification						
Anencephaly	1,092,853	85	40	0	125	1.1 (0.9, 1.3)
Spina bifida	1,092,853	179	43	166	388	3.5 (3.2, 3.9)
Encephalocoele	1,092,853	27	8	36	71	0.7 (0.5, 0.8)
Total	**1,092,853**	**291**	**91**	**202**	**584**	**5.3 (4.9, 5.8)**

Notes

(a) Number of total births in participating jurisdictions. These include modified material based on Australian Institute of Health and Welfare and University of New South Wales material published in 'Australia's mothers and babies' reports for the years 2007 to 2011 (Laws et al, 2009, Laws et al 2010, Laws et al 2011, Li et al 2012, Li et al, 2013). **Source data for these reports from:** Australian Institute of Health and Welfare (AIHW)National Perinatal Data Collection. Details of the collection retrieved 25 February 2016 from http://www.aihw.gov.au/mothers-and-babies/;

(b) NTD birth outcomes comprise stillbirths (SB), neonatal deaths (NND) and neonatal survivors (NNS).

(c) NTD birth prevalence (95% confidence intervals) per 10,000 total births.

n.p. Not presented - one or more cells with values of 3 or less.

Discussion

Overall reduction in NTD rates

This report has found reductions in the NTD rate for babies conceived in the standard period following the introduction of the mandatory folic acid fortification standard compared with babies conceived in the baseline period before the standard was implemented. For the total study population, comprising residents of New South Wales, Queensland, Western Australia, South Australia and the Northern Territory the reduction in rates of NTD between the baseline period and the standard period was 14.4% (95%CI 0.7% to 26.2%) and statistically significant. In the population omitting residents of New South Wales, reduction in the rates of NTD between the baseline period and standard period was 12.5% (95%CI -4.7, 28.9) and not statistically significant. These levels of reduction are within the predicted range of NTD reduction (Bower et al. 2006). The folic acid fortification standard was expected to prevent between 14 and 49 out of 300 to 350, NTD pregnancies (FSANZ 2006), a reduction in NTD rates of 4% to 16%.

The reduced NTD rates over this study period from 2007 to 2011 need to be viewed in the context of already declining NTD rates. The decline since the mid-1990s continued up to 2008. These are evident in individual jurisdictional reports that have long time series in Victoria (Riley and Halliday 2008),South Australia (Gibson et al. 2015) and Western Australia (WARDA 2015) as well as those collated from these states in earlier national reports (Abeywardana and Sullivan 2008, Macaldowie and Hilder 2011). Estimates of the level of the decline in the years up to 2008 vary depending on the time period chosen. Further differences appear with a different jurisdictional mix, as evident when the NTD rates in Queensland, Western Australia, South Australia and the Northern Territory from this study are contrasted with those reported earlier from Victoria, Western Australia and South Australia. It is therefore not possible to make an arithmetical adjustment to account for the background decline in NTD rates at this stage. The background level of NTD reduction would be expected to continue and it may be possible in the future to assess the background level of decline in NTD rates in this population.

Strengths and limitations

The study benefits from having obtained all the available data on NTD in Australia for the period 2007 to 2011. This is the first time that data from Queensland and the Northern Territory have been used in combination with data on congenital anomalies among births and pregnancies that ended with a termination of pregnancy before 20 weeks gestation. The NTD rate definition used in the study was equivalent to measures referred to in other national and international reports as the ‘prevalence of NTD’ or the ‘overall NTD prevalence’ (Dolk et al. 1991, ICBDSR 2010, Macaldowie and Hilder 2011).

Jurisdictional rates of NTD across the whole study period were somewhat lower in Queensland and the Northern Territory than in Western Australia and South Australia and substantially lower in New South Wales and Tasmania. Data from New South Wales are known to have less complete ascertainment of NTD (Centre for Epidemiology and Evidence 2012) and this was considered to occur largely because of differences in data collection practices. Lower ascertainment may also result from the loss of data for NTD-affected babies of women travelling interstate to non-participating states and territories. The absence of data from Victoria is significant in this regard. As well as accounting for about one-quarter of Australia’s maternity population (Li et al. 2013),women are known to travel to Victoria for late termination of pregnancy (Hilder et al. 2014, deCosta and Douglas 2015).

In theory, the best estimates of NTD rates would be obtained by using data from Western Australia and South Australia, which are considered to have near complete ascertainment of congenital anomalies. However, these jurisdictions have relatively small populations and are more prone to random fluctuations (Abeywardana and Sullivan 2008). In South Australia, a spike in the NTD rate in

2009 and 2010 with NTD rates of 18.4 per 10,000 total births in 2009 and 19.4 per 10,000 total births in 2010 was extensively investigated (Flood et al. 2013). This was partially explained by an increase in cases among young women of North African origin. This increased NTD rate in South Australia had subsequently decreased to 10.5 per 10,000 births in 2011, a rate that is lower than in 2008. In Western Australia the NTD rate peaked at 14.3 per 10,000 births in 2011 (Table 6). This was also reported in Western Australia, but NTD rates fell subsequently to new lows of 11 per 10,000 births in 2012 and 10 per 10,000 births in 2013 (WARDA 2015). Large populations are required to produce stable estimates of the occurrence of rare conditions such as NTD. Population sub-samples may be subject to random variation and caution is required when interpreting such data.

However, the focus of this report is the comparison of NTD rates before and after introduction of the mandatory folic acid fortification standard. Although data collection practices varied between jurisdictions, there was no change in collection practices within individual jurisdictions over time. The Western Australia Register of Developmental Anomalies became a statutory register from 2011 (WARDA 2015). Despite spikes in NTD in South Australia and Western Australia in 2010 and 2011 the NTD rate among conceptions fell over time for the total study population. The NTD rate among births in New South Wales was notably lower in 2011 (4.6 per 10,000 births) than in earlier years. However, the level of ascertainment in New South Wales was unchanged in the years of this study from those in previous years and annual NTD rates in this state are also subject to random variation. The NTD rate in 2012 was 5.3 per 10,000 births (NSW Ministry of Health, unpublished data). NTD rates in New South Wales may be more sensitive to effects of changes over time among younger women and women of Aboriginal and Torres Strait Islander origin, who are more likely to have their pregnancies managed in the public sector. There is no information currently available to determine whether the levels of interstate travel to Victoria by women diagnosed with as having an NTD affected pregnancy changed over the course of this study.

Analysis omitting New South Wales from the study population was undertaken as a sensitivity analysis. This addressed the potential bias of missing data from this state which contributes a third (32.9%) of the NTD-affected babies in the study. Inclusion of New South Wales provides a much larger population and improved the study power.

The use of pregnancy start rather than pregnancy end for both numerator (NTD-affected babies) and denominator (total births) preserves the relationship between NTD-affected babies and total births in a specified period, allowing for direct comparison of NTD rates among conceptions with NTD rates among births. Furthermore, comparing conceptions that resulted in a birth rather than births allowed for a more efficient use of the data than methods in previous reports which used annual rates of NTD in relation to births. Thus, data for 282 conceptions of NTD-affected babies from the total study populations of New South Wales, Queensland, Western Australia, South Australia and the Northern Territory in the period after introduction of the fortification standard period were available compared to 180 NTD-affected babies from births or terminations of pregnancy in 2011. The number of NTD-affected babies not able to be counted because of ambivalent exposure to foods fortified under the mandatory standard was also lower: 153 conceptions of NTD-affected babies were assigned for the transition period, compared with 433 babies born in 2009 and 2010.

The data did not enable distinction between occurrent and recurrent cases of NTD because pregnancies for the same women are not identified. The first NTD-affected baby for a specified woman would be identified as an occurrent case. A second and any subsequent NTD-affected baby would be identified as a recurrent case. This distinction is important for clinicians and measures of NTD incidence in women or families, but is not needed to calculate or compare population NTD rates over time.

To conform to the ICBDSR definition, this study rejected three NTD cases reported from pregnancies that ended in spontaneous miscarriage. NTD from spontaneous miscarriages are not counted even

though NTD are relatively more common among such pregnancies (Creasy and Alberman 1976), because as a rule these pregnancies are not scrutinised for the presence of congenital anomalies.

Isolated NTD

It is generally assumed that folate insufficiency is more likely to result in isolated NTD and that folic acid supplementation and fortification will reduce isolated NTD and have little or no effect on syndromal or multiple defect categories. In the United States, the proportion of isolated spina bifida decreased (from 83% to 72%), while the proportion of non-syndromal and non-isolated spina bifida increased (from 17% to 28%) in pre- and post-mandatory fortification periods (Parker et al. 2014). No such change was evident in the present study.

Non-isolated NTD reported in this study combined syndromal and multiple defect categories into a single category. These were identified by classifying all non-NTD conditions that were reported to distinguish conditions related to the NTD (Rasmussen et al. 2003) from conditions that had no known relationship to NTD.

It is possible that reporting of non-NTD anomalies is incomplete in the present study. Among NTD-affected babies from pregnancy terminations before 20 weeks gestation, 10.3% were classified as non-isolated NTD while for other pregnancy outcomes the proportion of non-isolated NTD ranged from 19.7% to.24.4% (Appendix E table E6). This may reflect different standards for examination and diagnosis of anomalies in these babies compared with babies from pregnancies ended as live births or stillbirths. Reliance on ultrasound findings alone for diagnosis may increase the potential to miss other conditions from pregnancies that ended in termination. Karyotyping of apparently isolated NTD found on ultrasound showed that 16% had unrecognised chromosomal anomalies (Harmon et al. 1995). More rigorous and systematic investigation at source may be required to improve the quality of information needed to properly distinguish isolated and non-isolated NTD.

Reduced NTD among babies of Indigenous women

The scale of the decline in the NTD rate among babies of women of Aboriginal or Torres Strait Islander origin was not anticipated. Higher NTD rates have been consistently found for these babies compared with babies of non-Indigenous women in earlier reports. Furthermore, these reports show that from 1992, when strategies to increase periconceptional folic acid consumption had been implemented, there had been no reduction in NTD rates among babies of Indigenous women compared with declines in NTD rates among babies of non-Indigenous women. The NTD rates for babies of women of Aboriginal or Torres Strait Islander origin in the baseline period in this study are comparable with NTD rates from earlier studies.

Ethnic differences in the impact of mandatory fortification and NTD rates have been reported (Dolk et al. 1991, Williams et al. 2005). In the United States, folic acid fortification has resulted in less disparity between ethnic groups, with the higher rates among Hispanic and non-Hispanic white populations prior to mandatory fortification more closely approximating the lower NTD rates among non-Hispanic black populations thereafter. In this study, the NTD rates (or risk) for babies of Aboriginal or Torres Strait Islander women declined following the introduction of mandatory fortification. This is the first time that a reversal in the profile of NTD risk has been observed. The differences between the two periods are statistically significant, so they are unlikely to be a chance finding. Further, they are evident both for the populations including and omitting New South Wales.

Further investigation and a longer time series post fortification are needed to confirm and explain these findings.

Reduced NTD rates among teenagers

Young women have been recognised as a particularly difficult group to reach through health education because of the high number of unplanned pregnancies, which limits the potential of the success of changes to folic acid consumption from periconceptional supplementation (Stockley and Lund 2008). Lower income and lower educational attainment have also been considered as reasons for the poorer response to dietary advice and supplements in order to increase folic acid consumption before and during the first 4 weeks of pregnancy (Bower et al. 2005).

This study found that the introduction of mandatory folic acid fortification of staple foodstuff was associated with the first documented substantial fall in the rate of NTD among babies of teenage women in Australia. The 54.8% fall in the NTD rate in the total teenage population is substantial and reverses earlier trends. While rates of NTD fell among older women in the years up to 2008, NTD rates among teenagers rose between 2000 and 2008 (Macaldowie and Hilder 2011).

Increased NTD rates among older women

The statistically non-significant increases in the rate of NTD among women aged 35 years or older who conceived a pregnancy in the standard period that continued to a birth was seen in the total study population and the population omitting New South Wales. Further, the rates of isolated NTD in the baseline period showed a strong positive gradient with increasing maternal age, but no change with maternal age in the standard period, after mandatory folic acid fortification had been introduced.

Several factors could contribute to these findings. Older women may have been more responsive than younger women to advice to increase periconceptional folate intake. If by the time the mandatory folic acid fortification standard was introduced most of the older women who were becoming pregnant were already consuming sufficient folates,(either from diet or as supplements), mandatory fortification would be expected to have a limited effect in this group. Other known causes of NTD are less common, but more likely to affect older women. These may be driving the increase in NTD rates observed in the standard period among women aged 35 or older. However, as this study did not collect information on maternal risk factors, it was not possible to test these assertions. These findings do not detract from the significance of folic acid protection against NTD.

Folate testing for women of reproductive age

The World Health Organisation has recently released evidence-based recommendations on blood folate concentrations in women of reproductive age that examines the utility of red blood cell and serum folate as biomarkers in population level assessment of NTD risk (WHO 2015). The guideline recommends that red blood cell folate threshold of 400ng/ml in women of reproductive age can be used as an indicator of folate sufficiency at the population level. Measurement of red blood cell folate to test the assertion that women over the age of 35 have higher intakes of folates, would complement investigation of other risk factors that could explain the increased rates of NTD observed in this group. Studies of red blood cell folate and its relation to serum folate could supplement the findings from the current report for NTD rates among teenagers and women of Aboriginal or Torres Strait Islander origin. Women in both these groups appear to have reached the nadir rate of less than 8 NTD per 10,000 births (WHO 2015).

Reduced birth prevalence of NTD after mandatory folic acid fortification

Birth prevalence rates are determined both by the rate of NTD among all pregnancies and the rate of pregnancy termination for NTD before 20 weeks gestation. In the five states and territories for which NTD data were ascertained, both from births and terminations of pregnancy, there was no apparent increase in termination of NTD-affected pregnancies over time or in 2011(Bower et al. 2004,

Abeywardana and Sullivan 2008, Macaldowie and Hilder 2011). The reduced birth prevalence appears to have resulted from primary prevention of NTD rather than increased use of TOP.

Reduced NTD rates following introduction of the mandatory folic acid fortification standard translated into a 10.9% lower birth prevalence of NTD in 2011 compared with 2007–2008 (5.6 versus 4.9 per 10,000 total births respectively).

Conclusions

This study found reductions of a statistically significant14.4% (95%CI 0.7, 26.2) in NTD rates for babies conceived in the period after introduction of the mandatory folic acid fortification standard relative to the baseline period for the total study population comprising residents of New South Wales, Queensland, Western Australia, South Australia and the Northern Territory. A similar, but statistically non-significant reduction of 12.5% (95%CI -4.7, 28.9) for the population omitting residents of New South Wales, where NTD rates fell from 12.8 per 10,000 conceptions (95%CI 11.4, 14.4) in the baseline period to 11.2 NTD per 10,000 conceptions (95%CI 9.7, 12.8) in the standard period. These reductions are in keeping with the predicted reduction in NTD of 4% to 16% for the level of folic acid fortification introduced.

This report provides evidence of reduced rates of NTD following the introduction of the mandatory folic acid fortification standard. This is seen in the context of a localised spike in NTD rates in South Australia in 2009 and 2010 and Western Australia in 2011. The reductions are at the upper level of predicted range, but some of this reduction is likely to reflect background declines in NTD.

Furthermore, a substantial reduction in the NTD rate was evident among groups in the population who had previously been found to have a higher prevalence of NTD-affected babies: teenagers and women of Aboriginal or Torres Strait Islander origin. This suggests that a more equitable and whole of population reduction in NTD has been achieved.

These results need to be considered in the context of the short post-fortification period for which study data were available and the relative rarity of NTD both of which contribute to variability in NTD rates. Ongoing monitoring of NTD rates post-fortification will be required to confirm that these reductions in NTD rates are sustained.

These results do not prove that mandatory fortification caused the reduction of NTD. They need to be viewed in the context of other studies that measure the direct effects in individuals of mandatory folic acid fortification and information about the extent and reach of ongoing voluntary folic acid fortification of foods within the target population.

Appendix A: Data sources

Note that the terms 'congenital anomaly', 'developmental anomaly' and birth defect' are synonymous and can be used interchangeably.

Congenital anomaly registers

The **Western Australia Register of Developmental Anomalies (WARDA)** includes congenital anomalies diagnosed prenatally and in children up to six years of age. The definition of a birth defect for the purposes of the WARDA is 'a structural or functional abnormality that is present at conception or occurs before the end of pregnancy and is diagnosed by six years of age'. Notification is statutory. Validation studies in Western Australia have shown the register to be near complete (Bower et al. 2000, Bower et al. 2001). Notification to the WARDA became statutory in 2011.

WARDA has a commitment to obtain high-quality, complete and population-based information on birth defects and cerebral palsy for Western Australia, and to use this information:

- to monitor the number of cases of developmental anomaly in Western Australia
- to plan, monitor and evaluate services for the prevention and alleviation of developmental anomalies and the care of persons with a developmental anomaly in Western Australia
- to compile and publish general or statistical information relating to developmental anomalies
- to carry out research into the causes of developmental anomalies and the effectiveness of prevention, screening and treatment services.

The **South Australian Birth Defects Register (SABDR)** benefits from legislation mandating the notification of congenital anomalies in pregnancies irrespective of gestational age and in children up to five years of age. South Australian data is considered almost complete.

SABDR is a population-based collection of information on birth defects, including cerebral palsy. The Register collects information on all children born in South Australia on or after 1 January 1986 who have a significant birth defect detected in the first five years of life. It thus complements and extends the collection of congenital abnormalities detected in the perinatal period and notified by doctors to the Pregnancy Outcome Unit of South Australia Health.

The Register defines a birth defect as 'any abnormality, structural or functional, identified up to five years of age, provided that the condition had its origin before birth'.

The Register includes:

- terminations of pregnancy at any gestation performed because of a diagnosis of a birth defect
- stillbirths and newborn babies with birth defects
- children diagnosed with a birth defect after the neonatal period and prior to their fifth birthday.

The Register is located in the Women's and Children's Hospital in the Health Informatics, Performance, Planning and Outcomes Unit. This is an ideal location for the following reasons:

- The majority of children with birth defects requiring medical or surgical care are referred to the Women's and Children's Hospital for assessment or further management at some stage.
- The major paediatric diagnostic services and perinatal/paediatric pathology services are located at the Women's and Children's Hospital.

The New South Wales **Register of Congenital Conditions (RoCC)** reports congenital anomalies detected during pregnancy or at birth, or diagnosed in infants up to one year of age.

From 1 January 1998, doctors, hospitals and laboratories have been required under the New South Wales *Public Health Act 1991* to notify certain congenital conditions detected during pregnancy or in a baby up to one year of age. Information reported is included in the New South Wales Register of Congenital Conditions, formerly known as the New South Wales Birth Defects Register.

There are three types of conditions that are reported to the Register:

- structural conditions that affect the growth, development and health of the baby that are present before birth, such as neural tube defects, cleft lip, dislocated hip and problems with the development of the heart, lungs or other organs
- conditions due to changes in the number of the baby's chromosomes, such as Down syndrome
- specified medical conditions: cystic fibrosis, phenylketonuria, congenital hypothyroidism and thalassemia major.

Notifications can be made electronically or using a paper form. The form for notifying a condition in an infant is used for conditions diagnosed in a live born infant up to the age of one year or a stillborn infant. Notifications of congenital conditions diagnosed antenatally in the fetus are required even if the pregnancy continues. More than one notification may be received for any one baby.

Data were requested from the **Victorian Congenital Anomalies Register** for this study, but data could not be provided for the study.

The Victorian Congenital Anomalies Register (formerly the Victorian Birth Defects Register) was established in 1984 under the auspices of the Consultative Council on Obstetric and Paediatric Mortality and Morbidity, which is the advisory body to the Victorian Minister for Health on maternal, perinatal and paediatric mortality and morbidity. The register collects data on congenital anomalies for all live births, stillbirths and terminations of pregnancy irrespective of age at diagnosis, with a period of detection up to 18 years of age. Data are obtained from multiple sources including the Victorian Perinatal Data Collection (birth notifications), hospital sources, perinatal death certificates, autopsy reports, cytogenetics reports and voluntary notifications from maternal and child health nurses and other professionals or community members. Following the transition to electronic reporting of perinatal data, there has been a disruption to the reporting of Victorian congenital anomalies from 2010, and the reporting of congenital anomalies in Victoria is currently under review. A report containing data on congenital anomalies in Victoria from 2007–09 will be available later in 2015.

The **Queensland Birth Defects Register** collates information for congenital anomalies reported in the perinatal period among live births and stillbirths from the Queensland Perinatal Data Collection and supplemented with information about these deaths from hospital inpatient data, death certification and autopsy reports.

Other jurisdictional perinatal data sources

Routine data collections in all states and territories capture information about women who have an NTD-affected pregnancy or the birth of an NTD-affected baby:

1. *Perinatal data collections (PDC)*
   Notification of details of all births, both live births and stillbirths of at least 20 weeks gestational age or weighing 400g at birth to jurisdictional health authorities is required in all jurisdictions (Laws et al. 2011). The data include demographic information about the mother, and details of the pregnancy and birth, including gestational age of the baby at birth. All collections, except the Australian Capital Territory (Li et al. 2012), include some information about congenital anomalies evident at birth. NTD are visible anomalies and are unlikely to be

missed by the birth attendant. The exception is spina bifida occulta, which is not in the scope of NTD considered in this study (Table 1). Information about congenital anomalies evident at birth is collected in all jurisdictions. Details are included in the PDC in Queensland, New South Wales, Western Australia and South Australia, notifications are forwarded to the congenital anomaly register.

2. *Admitted patient data (APD)*
   Records of hospital episodes of care including overnight and day stays contain demographic and administrative data as well as data on the diagnoses and procedures carried out (AIHW 2012). Diagnoses and procedures have since 1998 been coded using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM) and the Australian Classification of Health Interventions (ACHI) respectively (NCCH 2010). Demographic information includes patient date of birth, Indigenous status and area of usual residence from which remoteness of residence can be derived. ICD-10-AM codes (O09.0–O09.7) provide information about pregnancy gestation.

3. *Perinatal death review (PDR)*
   Information is collected to support the review of perinatal deaths and include the findings of multidisciplinary committees in all states and territories. In the Northern Territory, over the reference years for this study, reviews were carried out only for babies who died in tertiary hospitals and there is no formal data collection. The high mortality of NTD-affected babies (Laws et al. 2010) make these records a valuable validation resource, particularly for stillbirths which otherwise rely solely on perinatal ascertainment.

4. *Registrations of births and deaths (RBD)* by Registrars of Births, Deaths and Marriages include information from the medical certificate of cause of death or cause of perinatal death. Access to these data by health authorities is by arrangement with the Registrar.

Queensland Admitted Patient Data Collection congenital anomalies (QAPDC-CA)

In Queensland, a process has been instituted to collect additional information about congenital anomalies among pregnancies that ended before 20 weeks gestation. The Queensland Health Admitted Patient Data Collection congenital anomaly dataset (QHAPDC-CA) forms a separate table that relates diagnostic data about each fetus with congenital anomaly with the relevant hospital episode for the pregnant woman. An automated request for information from the admitting facility is triggered by diagnostic codes in a woman's record that relate to confirmed or suspected fetal or placental anomaly combined with a ICD10-AM codes for abortive outcome and gestation less than 20 weeks.

Denominator data

The Australian Institute of Health and Welfare (AIHW) National Perinatal Data Collection (NPDC) includes information about all births from pregnancies that continued to 20 or more weeks gestational age or with at least one baby who weighed 400 g or more at birth. Information about state of usual residence, date of birth and gestational age at birth maternal age, birth multiplicity and maternal Indigenous status all collected as using nationally standard data items and are relatively complete for the years 2007–2011. Gestational age at birth is collected as completed weeks using the best estimate of gestational age available for each birth.

Tabulated data for residents for the five states and territories whose data were used to calculate NTD rates were requested stratified by maternal age, maternal Indigenous status and birth multiplicity using the AIHW portal.

Rules for deriving estimated date of conception were provided with the data request, and month and year of conception were derived in the same way as data for NTD babies.

Appendix B: Ethics approvals

Jurisdiction	Committee	Status	Reference number [submission code]
Institutional[(a)]	University of New South Wales (UNSW) Human Research Ethics Committee (A) (EC00397)	Approved. 11/11/2013	HC13311
NSW	NSW Population and Health Service Research Ethics Committee (EC00410)	Approved. 08/01/2014	HREC/13/CIPHS/61 Cancer Institute NSW reference number: 2013/11/491
	(NSW) Aboriginal Health & Medical Research Council Ethics Committee (EC00342)	Approved. 20/02/2014	991/13
Qld	Queensland Health Office of Health & Medical Research –Human Research Ethics Committee (EC00334)	Approved. 25/11/2013	HREC/13/QHC/39
WA	Department of Health WA Human Research Ethics Committee (EC00422)	Approved. 05/12/2013	2013/69
	Western Australia Aboriginal Health Ethics Committee (EC00292)	Approved. 05/02/2014	547
SA	SA Department of Human Research Health Ethics Committee (EC00304)	Approved. 20/12/2013	[AU/1/43E112]
	(SA) Aboriginal Health Research Ethics Committee (EC1085)	Approved. 12/12/2013	04-13-539
Tas	Tasmania Health & Medical Human Research Ethics Committee (EC00337)[(b)]	Approved. 05/02/2014	H0013702
NT	Human Research Ethics Committee of Northern Territory Department of Health and Menzies School of Health (EC00153)	Approved. 02/12/2013	HoMER 13-2100

Notes

(a) The University of NSW HREC (A) is the primary ethics committee providing the overarching review of the project from a national perspective.

(b) HREC will endorse primary ethics committee approval. Application was made to the committee applying this principal.

Appendix C: Minimum dataset

The following data were requested from all participating states and territories.

Pregnancy (mother) id number[a]
Sequence number (birth order)[b]

- Type(s) of NTD –coded to ICD-10-AM, ICD-9-BPA or as free text
- Other congenital anomalies –coded to ICD-10-AM, ICD-9-BPA or as free text
- Month/year of birth or termination of pregnancy (TOP)
- Estimated date of conception(c): month and year; or
  - Estimated date of delivery (EDD)[d]; or
  - Full date of birth/TOP[d]
- Mother's age (years, aggregating data for ages <20, ≥40)
- Pregnancy outcome (TOP/Birth)
- Baby survival (SB, LB, NND)
- Gestational age at birth/TOP
- Birth/fetal weight (100g groups, aggregating data for weights <1,000g and ≥4,000g)
- Baby/fetal sex (male, female, indeterminate)
- Birth/pregnancy plurality
- Indigenous status of mother
- State of usual residence
- SLA of usual residence /Postcode, if missing SLA
- AGSC/AGCS code for remoteness weightings
- SEIFA score for relative disadvantage (national decile) weightings.

Notes

a) The same number should be given for mothers of babies from a multiple birth. Repeated subsequent pregnancies for the same mother should be given separate **Pregnancy (mother) id numbers**.

b) Sequence number (birth order) will be 1 for a baby/fetus from singleton pregnancies. Pregnancy (mother) id + Sequence number (birth order) uniquely identified each baby/fetus.

c) EDD or 'Full date of birth/TOP' are required if 'Estimated date of conception' cannot be provided. 'Estimated date of conception' can be calculated using one of the formulas below:

- Expected date of delivery (EDD) minus 266; or
- Date of birth/date of TOP minus days of gestational age (days) plus14; or
- Date of birth/date of TOP minus weeks of gestational age (completed weeks) plus17.

d) EDD and date of birth/TOP are requested only if estimated date of conception cannot be supplied. This is to derive estimated date of conception (MMYYYY) after which these dates will be removed from the working data.

Appendix D: Data preparation and assessment of data quality

Records received

Information about 1,039 NTD among pregnancies ending in a birth or a termination of pregnancy for congenital abnormality were obtained from New South Wales, Queensland, Western Australia, South Australia, Tasmania and the Northern Territory. Anomalous records were queried with the Data Manager in the relevant jurisdiction and resolved prior to collating the data. Each dataset was read into Statistical Analysis Software (SAS) applying standard variable names and formats and combined into a single dataset.

Information was requested about all congenital conditions identified in NTD-affected babies. This was provided as ICD-9-BPA coded conditions for records from Western Australia, South Australia and New South Wales, ICD-10-AM coded data for records from Queensland and free text fields for records from the Northern Territory and Tasmania. Text fields were manually assigned an ICD-9-BPA code and ICD-9-BPS to ICD-10-AM (5th edition) Mapping Tables were used to assign one or more ICD-9-BPA codes.

Records that did not comply with study definitions, or for pregnancies that ended before 2007 or after 2011, were flagged (Table D1) and excluded from further analysis. Three NTD-affected babies from New South Wales were identified from pregnancies ending as spontaneous abortions and one baby from Tasmania was diagnosed as having spina bifida occulta. The five 'out-of-period' records were pregnancies ending in 2012 and 2013.

Table D1: Reason for exclusion of reported NTD cases

Reason for exclusion	State/territory of origin of record						
	WA	SA	NT	Qld	NSW	Tas	Total
				Number			
None	204	143	19	311	337	16	1,030
Out of period [(a)]	0	0	0	0	1	4	5
Not compliant[(b)]	0	0	0	0	3	1	4
Total	**204**	**143**	**19**	**311**	**341**	**21**	**1,039**

Notes

(a) Out-of-period records for pregnancies ended after 2011.
(b) Not compliant with study definitions

Data quality

The search for duplicated NTD cases was negative, but duplicate mother details were found indicating a twin pregnancy with both babies affected by NTD.

There were no substantial differences between the estimated dates of conception calculated by source data providers and those calculated using gestational age and data of birth data provided to the study, recognising that small discrepancies may arise because of confidentialisation of dates of birth and less precise gestational age data provided to researchers.

The 1,030 included records were examined for completeness and data quality of key data items: estimated date of conception, gestational age, maternal Indigenous status, maternal age and multiple birth. Table D2 shows that missing data were primarily from New South Wales and were most commonly found among live birth survivors (Table D3). Estimated date of conception was missing for 38 (3.7%) of records, mostly from New South Wales.

Table D2: Number of study records with incomplete data values, by state of origin of record

Data items	WA	SA	NT	Qld	NSW	Tas	Total
				Number			
Study period	0	0	1	0	7	4	12
Estimated date of conception	0	0	1	0	33	4	38
Gestational age	2	0	0	0	18	0	20
Maternal Indigenous status	2	0	0	4	44	16	66
Maternal age	0	0	0	0	78	0	78
Multiple birth	0	0	0	0	0	0	0
Any missing data	3	0	1	4	91	16	115
No missing data	201	143	18	307	246	0	915
Total	**204**	**143**	**19**	**311**	**337**	**16**	**1,030**
				Per cent			
Study period	..	..	5.3	..	2.1	25.0	1.2
Estimated date of conception	0.0	0.0	5.3	0.0	9.8	25.0	3.7
Gestational age	1.0	0.0	0.0	0.0	5.3	0.0	1.9
Maternal Indigenous status	1.0	0.0	0.0	1.3	13.1	100.0	6.4
Maternal age	0.0	0.0	0.0	0.0	23.1	0.0	7.6
Multiple birth	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Any missing data	1.5	0.0	5.3	1.3	27.0	100.0	11.2

Table D3: Number of study records missing data, by pregnancy outcome

	Pregnancy outcome					
Key data items	NNS	NND	SB	SB-T	TOP	Total
			Number			
Estimated date of conception	23	2	4	6	15	38
Gestational age	17	0	0	0	3	20
Maternal Indigenous status	16	2	6	6	36	66
Maternal age	47	2	3	0	26	78
Multiple birth	0	0	0	0	0	0
Any missing data	55	4	7	6	43	115
No missing data	148	86	194	84	403	915
Total	**203**	**90**	**201**	**90**	**446**	**1,030**
			Per cent			
Estimated date of conception	11.3	2.2	2.0	6.7	3.4	3.7
Gestational age	8.4	0.0	0.0	0.0	0.7	1.9
Maternal Indigenous status	7.9	2.2	3.0	6.7	8.1	6.4
Maternal age	23.2	2.2	1.5	0.0	5.8	7.6
Multiple birth	0.0	0.0	0.0	0.0	0.0	0.0
Any missing data	27.1	4.4	3.5	6.7	9.6	11.2

Abbreviations: NNS = Neonatal survivor; NND = Neonatal death; SB = stillbirth; SB-T = termination of pregnancy in stillbirths are terminations carried out after 20 weeks; TOP = termination of pregnancy.

Manual assignment of study period

For 26 of the 33 records from New South Wales where estimated date of conception was missing, it was possible to assign a study period in which the conception occurred based on the date of birth or termination of pregnancy in the absence of gestational age or for gestational age and the year of registration and pregnancy outcome provided with the New South Wales data for this for all cases.

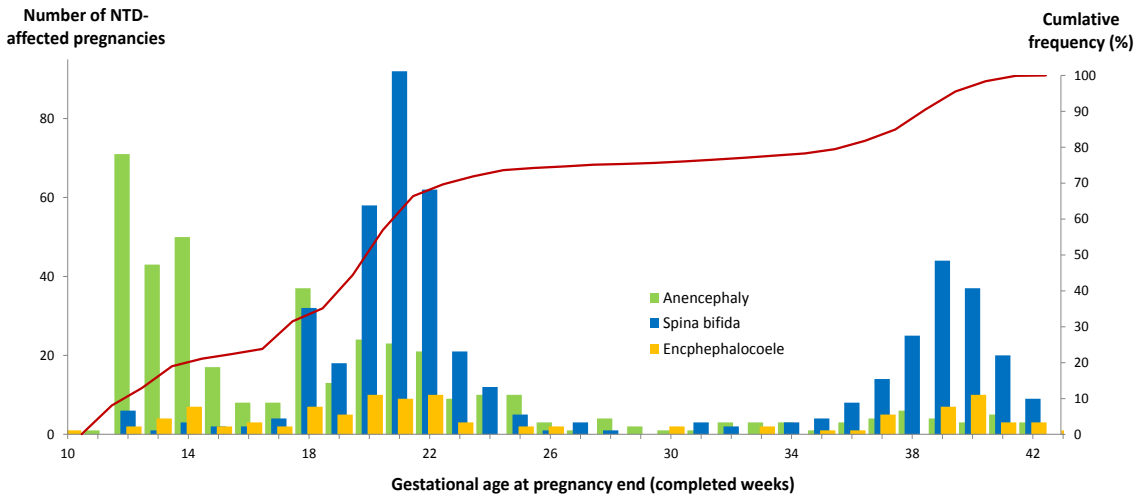
Gestational age

Gestational age measures pregnancy duration and here refers to the duration of the completed pregnancy. The distribution of the gestational ages for the 1,030 study babies with NTD ranged from 10 weeks to 42 weeks, with a median gestational age of 20 weeks (Figure D1). By 28 weeks gestation, the pregnancy had been completed for three-quarters of the study babies.

Babies with anencephaly had the shortest pregnancies with a median gestation of 16 weeks, while spina bifida and encephalocoele both had a median gestation of 20 weeks.

All types of NTD peaked at gestational age corresponding broadly with the gestations recommended for anomaly scans at 14 and 18 weeks gestation.

Figure D1: Gestational age at pregnancy end, by NTD classification



NTD data quality

Ascertainment of NTD from pregnancies terminated before 20 weeks gestation is more complex than from pregnancies that end with a birth, particularly in states and territories that do not have statutory collection of data about pregnancy terminations. Anencephaly is more visible than spina bifida on early ultrasound scans that are performed at gestations when social termination of pregnancy is more easily available. The proportion of cases obtained from pregnancy terminations before 20 weeks gestational age and the ratio of spina bifida to anencephaly cases are used in combination as indicators of the completeness of ascertainment of NTD. Results for the study records obtained from each state or territory is shown in Table D5.

All NTD records from Tasmania were from pregnancies that ended as a birth and none were from pregnancies that ended as a termination before 20 weeks gestation. There were six spina bifida cases for every case of anencephaly in the Tasmanian data. New South Wales obtained just under one-third of the NTD cases from termination of pregnancy and had more than two spina bifida cases for every case of anencephaly. In Western Australian and South Australia, more than half of all NTD

records were from pregnancies that ended as a termination before 20 weeks gestation and there were almost equal numbers of spina bifida and anencephaly cases.

Table D4: NTD ascertainment, by state or territory of record origin

	WA	SA	NT	Qld	*NSW*	Tas	Total
				Number			
NTD classification[(a)]							
Anencephaly	85	68	12	146	87	2	400
Spina bifida	88	63	5	143	204	12	515
Encephalocoele	31	12	2	22	46	2	115
Pregnancy outcome							
Birth	94	57	10	180	232	16	589
TOP[(b)]	110	86	9	131	105	0	441
Total NTD	**204**	**143**	**19**	**311**	**337**	**16**	**1,030**
				Per cent			
TOP[(b)]	53.9	60.1	47.4	42.1	31.2	0.0	42.8
Anencephaly	41.7	47.6	63.2	46.9	25.8	12.5	38.8
				Ratio			
SBf:An[(c)]	1.04	0.93	0.42	0.98	2.34	6.00	1.29

Notes
(a) NTD classification assigns babies with multiple NTDs – refer to Table 3 for details of the classification.
(b) Termination of pregnancy.
(c) SBf:An is the spina bifida to anencephaly ratio.

Resident populations

NTD occur in the first 4 weeks of pregnancy. Neither congenital anomaly collections nor birth collections collect information regarding the whereabouts of women at the beginning of the pregnancy, but both collect area of usual residence. This was used as the proxy value for place of conception. Study records from each state or territory were distributed by state and territory of usual residence (see Table D5). Overall, 2% of babies with an NTD were not resident in the state or territory in which the defect was recorded. However, five (21%) NTD-affected babies among Northern Territory residents ended in another participating jurisdiction.

Table D5: Study babies, by state/territory of record origin and state/territory of residence

State of usual residence	State/territory of origin of record						
	WA	SA	NT	Qld	NSW	Tas	Total
				Number			
WA	202	..	..	..	..	..	**202**
SA	..	139	..	1	..	..	**140**
NT	..	2	19	2	1	..	**24**
Qld	1	..	..	305	3	..	**309**
NSW	..	1	..	1	330	..	**332**
Tas	1	0	..	..	..	16	**17**
Other[(a)]	..	1	..	2	3	..	**6**
Total	**204**	**143**	**19**	**311**	**337**	**16**	**1,030**

Note

(a) Other Includes residents of Victoria, ACT and Australian non-residents.

Babies that informed NTD rates

The 16 NTD babies from Tasmania (Table D5) were not included in data used to calculate NTD rates because NTD ascertainment in this state was only from births.

There was one additional NTD baby of a Tasmanian resident mother born in Western Australia and 6 NTD babies of residents of other states and territories who did not contribute to the calculation of NTD rates by maternal state of usual residence. Populations of NTD babies of residents of participating states and territories were further defined by the time periods in which they were conceived.

There were 14 NTD babies born in Queensland between January and June 2007. There were no data in this period about babies with NTD from the QHAPDC-CAD and therefore NTD rates could not be determined. The remaining 1,000 babies informed NTD rates among births by state of occurrence.

New South Wales cases were included for the calculation of NTD rates, but rates omitting New South Wales were also produced as these are better estimates of the absolute risk of NTD in this period. NTD rates omitting NSW also served as a sensitivity analysis to assess the potential for bias that could result from missing data.

Appendix E: NTD classified by co-existing non-NTD anomalies

Co-existing non-NTD conditions

Non-NTD conditions present in babies along with NTD were categorised as 'related to NTD' if the condition arose as a result of the presence of the NTD or as 'unrelated to NTD' if the condition was considered to have arisen separately from another cause. Where the cause of the co-existing condition is not well understood, the condition was categorised as having an 'uncertain relationship to NTD'. An existing schema categorising co-existing conditions according to the relationship with the NTD (Macaldowie and Hilder 2011) was applied to non-NTD conditions among the NTD affected babies in the study. The categories were checked and conditions not previously categorised were reviewed by two experts, one of whom had advised on the schema for the previous report. These lists are not exhaustive.

Tables E1 to E3 list co-existing conditions assigned as related, unrelated or having an uncertain relationship with the NTD. The tables list conditions specified by 5 digit codes if some, but not all the conditions with a fifth digit extension to the 4 digit code were assigned.

Table E1: Unrelated conditions, ICD-9-BPA codes and descriptions

Code	Description
743.22	Enlarged cornea
743.51	Specified anomalies of retina
743.60	Blepharoptosis
743.8	Other specified anomalies of eye
744.0	Anomalies of ear causing impairment of hearing
744.1	Accessory auricle
744.2	Other specified anomalies of ear
744.3	Unspecified anomaly of ear
744.4	Branchial cleft, cyst or fistula; preauricular sinus
744.5	Webbing of neck
744.8	Other specified anomaly of face and neck
745.0	Common truncus
745.1	Transposition of great vessels
745.2	Tetralogy of Fallot
745.4	Ventricular septal defect
745.5	Ostium secundum type atrial septal defect
745.6	Endocardial cushion defects
746.0	Anomalies of pulmonary valve
746.1	Tricuspid atresia and stenosis, congenital
746.2	Ebstein's anomaly
746.3	Congenital stenosis of aortic valve
746.4	Congenital insufficiency of aortic valve
746.5	Congenital mitral stenosis
746.6	Congenital mitral insufficiency
746.7	Hypoplastic left heart syndrome
746.8	Other specified anomalies of heart
746.9	Unspecified anomalies of heart
747.0	Patent ductus arteriosus
747.1	Coarctation of aorta
747.2	Other anomalies of aorta
747.3	Anomalies of pulmonary artery
747.4	Anomalies of great veins
747.5	Absence or hypoplasia of umbilical artery

747.6	Other anomalies of peripheral vascular system
747.82	Persistent fetal circulation
748.0	Choanal atresia
748.1	Other anomalies of nose
748.2	Web of larynx
748.3	Other anomalies of larynx, trachea, and bronchus
748.4	Congenital cystic lung
748.5	Agenesis, hypoplasia and dysplasia of lung
748.6	Other anomalies of lung
749.0	Cleft palate
749.1	Cleft lip
749.2	Cleft palate with cleft lip
750.1	Other anomalies of tongue
750.2	Other specified anomalies of mouth and pharynx
750.3	Tracheo-oesophageal fistula, oesophageal atresia and stenosis
750.70	Microgastria
751.0	Meckel's diverticulum
751.1	Atresia and stenosis of small intestine
751.2	Atresia and stenosis of large intestine, rectum, and anal canal
751.3	Hirschsprung's disease and other congenital functional disorders of colon
751.4	Anomalies of intestinal fixation
751.5	Other anomalies of intestine
751.6	Anomalies of gallbladder, bile ducts and liver
751.7	Anomalies of pancreas
752.0	Anomalies of ovaries
752.1	Anomalies of fallopian tubes and broad ligaments
752.2	Doubling of uterus
752.3	Other anomalies of uterus
752.4	Anomalies of cervix, vagina and external female genitalia
752.5	Undescended testicle
752.6	Hypospadias and epispadias
752.7	Indeterminate sex and pseudohermaphroditism
752.8	Other specified anomalies of genital organs
752.9	Unspecified anomaly of genital organs
753.0	Renal agenesis and dysgenesis
753.1	Cystic kidney disease
753.2	Obstructive defects of renal pelvis and ureter
753.3	Other specified anomalies of kidney
753.4	Other specified anomalies of ureter
753.5	Exstrophy of urinary bladder
753.6	Atresia and stenosis of urethra and bladder neck
753.7	Anomalies of urachus
753.8	Other specified anomalies of bladder and urethra
755.0	Polydactyly
755.1	Syndactyly
755.2	Reduction deformities of upper limb
755.3	Reduction deformities of lower limb
756.0	Craniosynostosis
756.1	Craniofacial dysostosis
756.2	Hypertelorism
756.3	Pierre Robin syndrome
756.4	Mandibulofacial dysostosis
756.5	Oculomandibular dysostosis
756.6	Goldenhar's syndrome
756.4	Chondrodystrophy
756.5	Osteodystrophies
756.6	Anomalies of diaphragm
756.7	Anomalies of abdominal wall
757.0	Hereditary oedema of legs

757.1	Ichthyosis congenita
757.3	Other specified anomalies of skin
757.4	Specified anomalies of hair
757.5	Specified anomalies of nails
757.8	Other specified anomalies of the integument
758.0	Down's syndrome
758.1	Patau's syndrome
758.2	Edward's syndrome
758.3	Autosomal deletion syndromes
758.4	Balanced autosomal translocation in normal individual
758.5	Other conditions due to autosomal anomalies
758.6	Gonadal dysgenesis
758.7	Klinefelter's syndrome
758.8	Other conditions due to sex chromosome anomalies
759.0	Anomalies of spleen
759.3	Situs inversus
759.6	Other hamartoses, not elsewhere classified
759.8	Other specified anomalies
759.90	Anomalies of umbilicus

Table E2: Related conditions, ICD-9-BPA codes and descriptions

Code	Description
742.1	Microcephalus
742.2	Reduction deformities of brain
742.3	Congenital hydrocephalus
742.4	Other specified anomalies of brain
742.5	Other specified anomalies of spinal cord
744.9	Unspecified anomalies of face and neck
754.0	Certain congenital musculoskeletal deformities of skull, face and jaw
754.1	Certain congenital musculoskeletal deformities of sternocleidomastoid muscle
754.2	Certain congenital musculoskeletal deformities of spine
754.3	Congenital dislocation of hip
754.4	Congenital genu recurvatum and bowing of long bones of leg
754.5	Varus deformities of feet
754.6	Valgus deformities of feet
754.7	Other deformities of feet
755.4	Reduction deformities, unspecified limb
755.5	Other anomalies of upper limb, including shoulder girdle
755.6	Other anomalies of lower limb, including pelvic girdle
755.8	Other specified anomalies of unspecified limb
755.9	Unspecified anomaly of unspecified limb
756.1	Anomalies of spine
756.2	Cervical rib
756.3	Other anomalies of ribs and sternum
759.1	Anomalies of adrenal gland
759.2	Anomalies of other endocrine glands
759.4	Conjoined twins
759.5	Tuberous sclerosis

Table E3: Uncertain conditions, ICD-9-BPA codes and descriptions

Code	Description
753.90	Unspecified anomaly of kidney
753.92	Unspecified anomaly of bladder
753.99	Unspecified anomaly of urinary system NOS
754.8	Other specified congenital musculoskeletal deformities
756.07	Localised skull defects
756.08	Other congenital musculoskeletal anomalies of skull and face bones
756.09	Unspecified congenital musculoskeletal anomalies of skull and face bones
756.8	Other specified anomalies of muscle, tendon, fascia and connective tissue

Classification of isolated NTD and non-isolated NTD

NTD were classified as 'isolated' if there were no unrelated conditions present and as 'non-isolated' if there was one or more unrelated conditions present. Related conditions could co-exist with either isolated or non-isolated NTD. If conditions with an uncertain relationship to NTD were present with unrelated conditions, the NTD were also classified as 'non-isolated'. However, if these were the only other conditions present or were present with related conditions, the NTD were classified as 'uncertain'. Table E4 summarises these criteria for classifying NTD as 'isolated', 'non-isolated' and 'uncertain'.

Table E4: Categorising isolated and non-isolated NTD

	Related	Unrelated	Uncertain
Isolated NTD	+/- conditions from table E2	No conditions from table E1	No conditions from table E3
Non-Isolated NTD	+/- conditions from table E2	At least one condition present from table E1	+/- conditions from table E3
Uncertain NTD	+/- conditions from table E2	No conditions from table E1	At least one condition from table E3

NTD-affected babes with isolated NTD and non-isolated NTD

NTD-affected babies into those with isolated NTD and non-isolated NTD and the presence within each of these categories of related anomalies is shown in Table E5. In total, 183 (17.8%) of the NTD in 1030 babies (all of the babies in scope for the study) were classified as non-isolated NTD and 80.1% were classified as isolated NTD. Only 22 (2.1%) of the 1,030 NTD cases could not be classified as isolated or non-isolated. Babies with non-isolated NTD (57.4%) were nearly three times more likely to have related anomalies than babies with isolated NTD (19.9%).

Encephalocoele was most likely the type of NTD to be classified as non-isolated NTD (32.2%), followed by spina bifida (19.0%) and anencephaly (12.0%), which was the least likely NTD type to be classified as non-isolated NTD.

The mix of NTD type differed within isolated NTD and non-isolated NTD groups. Just over half of all babies with isolated NTD had anencephaly (51.6%), a further 39.5% of babies had spina bifida the few remaining babies had encephalocoele (8.9%). Among non-isolated NTD spina bifida as the most common type of NTD, accounting for 53% and the remainder were split between anencephaly (26.2%) and encephalocoele (20.2%).

Table E5: Isolated and non-isolated NTD by presence of related anomalies and type of NTD, resident of NSW, Qld, WA, SA and NT

Type of NTD	Isolated NTD			Non-isolated NTD			Uncertain	Total
	No Related	Related	All	No related	Related	All		
				Number				
Anencephaly	341	10	351	27	21	48	1	400
Spina bifida	261	139	400	35	63	98	17	515
Encephalocoele	59	15	74	16	21	37	4	115
NTD	**661**	**164**	**825**	**78**	**105**	**183**	**22**	**1,030**
				Per cent				
Anencephaly			51.6			26.2		
Spina bifida			39.5			53.6		
Encephalocoele			8.9			20.2		
NTD			**100.0**			**100.0**		
NTD	80.1	19.9	**100.0**	42.6	57.4	**100.0**		
Anencephaly			87.8			12.0	0.3	100.0
Spina bifida			77.7			19.0	3.3	100.0
Encephalocoele			64.3			32.2	3.5	100.0
NTD			**80.1**			**17.8**	**2.1**	**100.0**

Babies with isolated and non-isolated NTD

Table E6 examines the characteristics of NTD-affected babies with isolated and non-isolated NTD and presents the proportion of babies in each group with non-isolated NTD. Non-isolated NTD appeared to be more common among the small number babies from multiple pregnancies (26.3%) than among singletons (15.9%), but this difference was not statistically significant. There were more non-isolated NTD among records obtained from Western Australia (21.1%) and New South Wales (19.7%) than from South Australia (14.0%) and Queensland (11.9%), but too few records from the Northern Territory or Tasmania for meaningful distributions of NTD by the co-existing anomaly. The 22 babies with uncertain NTD are not shown separately but are included in the total number of NTD-affected babies.

Only 10.3% of NTD babies from pregnancy terminations before 20 weeks gestation were classified as having non-isolated NTD while for other pregnancy outcomes the proportion of non-isolated NTD ranged from 19.7% to 24.4% (Table E6). This may reflect different standards for examination and diagnosis of anomalies in these babies compared with babies from pregnancies ended as live births or stillbirths.

Non-isolated required a documented co-existing anomaly that was not a consequence of the NTD. However, the absence of a co-existing NTD was inferred rather than having been positively documented. Overall, there were 661 babies who had NTD as the sole reported anomaly (Table E5). It is possible that some NTD were incorrectly classified as isolated NTD if co-existing anomalies were missed. This could occur if the record was incomplete, or if a less thorough pathological assessment was carried out. Nearly two thirds of all NTD-affected babies reported to the study had no evidence of the absence of a co-existing anomaly.

More focused and comprehensive assessment of the relationship of other conditions is needed to better characterise co-existent conditions.

Table E6: Characteristics of babies with isolated NTD and non-isolated NTD

	Isolated NTD	Non-isolated NTD	All NTD[(a)]	Non-isolated %	Non-isolated 95%CI
Maternal Indigenous status					
Aboriginal or Torres Strait Island	54	15	70	21.4	10.6 , 32.3
Non-Indigenous	734	140	894	15.7	13.1 , 18.3
Missing data	52	13	66	19.7	26.7 , 30.4
Maternal age (years)					
<20	44	10	55	18.2	6.9 , 29.5
20-24	130	30	163	18.4	11.8 , 25.0
25-29	216	33	252	13.1	8.6 , 17.6
30-34	239	40	286	14.0	9.6 , 18.3
35+	149	40	196	20.4	14.0 , 26.7
Missing data	62	15	78	19.2	9.5 , 29.0
Plurality					
Singleton	813	158	992	15.9	13.4 , 18.4
Multiple	27	10	38	26.3	10.0 , 42.6
Year of birth					
2007	154	39	198	19.7	13.5 , 25.9
2008	178	27	210	12.9	8.0 , 17.7
2009	177	41	223	18.4	12.8 , 24.0
2010	184	28	214	13.1	8.2 , 17.9
2011	147	33	185	17.8	11.8 , 24.0
Pregnancy outcome					
Neonatal survivor	150	40	203	19.7	13.6 , 25.8
Neonatal death	67	20	90	22.2	12.5, 32.0
Stillbirth	157	40	201	19.9	13.7 , 26.1
Stillbirth TOP	67	22	90	24.4	14.2 , 34.7
TOP	399	46	446	10.3	7.3 , 13.3
State of record origin					
NSW	270	65	337	19.3	14.6 , 24.0
Qld	257	37	311	11.9	8.1 , 15.7
WA	160	43	204	21.1	14.8 , 27.4
SA	121	20	143	14.0	7.9 , 20.1
NT	np	np	19	np	np
Tas	np	np	16	np	np
Total	**840**	**168**	**1,030**	**16.3**	**13.8 , 18.8**

Notes

(a) All NTD includes the 22 NTD-affected babies with classified as uncertain NTD co-existing anomaly whose relationship with NTD was uncertain

np Not presented. Preserves confidentiality, if small numbers

Appendix F: Tabulated results, total study population

Table F1: NTD rates among conceptions and change in NTD rates over time by type of NTD, residents of NSW, Qld, WA, SA and NT

Type of NTD	Study periods[a]			Change in NTD rates		
	Baseline	Transition	Standard			
			NTD-affected babies			
Anencephaly	191	51	112			
Spina bifida	218	87	141			
Encephalocoele	50	15	29			
NTD	**459**	**153**	**282**			
			Conceptions[b]			
	450,806	**163,072**	**323,507**			
		NTD rate[d]		*%diff[e]*	*RR[f]*	*RR 95%CI[g]*
Anencephaly	4.2	3.1	3.5	–18.3	0.82	0.647, 1.032
Spina bifida	4.8	5.3	4.4	–9.9	0.90	0.729, 1.114
Encephalocoele	1.1	0.9	0.9	–19.2	0.81	0.502, 1.277
NTD	**10.2**	**9.4**	**8.7**	**–14.4**	**0.86**	**0.738, 0.993**

Notes follow the final table in this section

Table F2: NTD rates among conceptions and change in NTD rates over time for NTD classified by co-existent anomaly, residents of NSW, Qld, WA, SA and NT

NTD classified by co-existing anomaly	Study periods[a]			Change in NTD rates		
	Baseline	Transition	Standard			
			NTD-affected babies			
Isolated	378	123	231			
Non-Isolated	69	29	44			
Uncertain	12	1	7			
Total NTD	**459**	**153**	**282**			
			Conceptions[b]			
	450,806	**163,072**	**323,507**			
			Per cent of total NTD			
Isolated	82.35	80.39	81.91			
Non-Isolated	15.03	18.95	15.60			
Uncertain	2.61	0.65	2.48			
		NTD rate[d]		*% diff[e]*	*RR[f]*	*RR 95%CI[g]*
Isolated	8.4	7.5	7.1	–14.8	0.85	0.723, 1.003
Non-Isolated	1.5	1.8	1.4	–11.1	0.89	0.609, 1.297
Total	**10.2**	**9.4**	**8.7**	**–14.4**	**0.86**	**0.738, 0.993**

Notes follow the final table in this section.

Table F3: NTD rates among conceptions and change in NTD rates over time by maternal age, residents of NSW, Qld, WA, SA and NT

Maternal age (years)	Study periods[a] Baseline	Transition	Standard		Change in NTD rates	
			NTD-affected babies			
<20	30	9	9			
20–24	79	27	39			
25–29	117	34	72			
30–34	121	45	81			
35+	75	33	64			
Missing data	37	5	17			
Total	**459**	**153**	**282**			
			Conceptions[b]			
<20	20,159	6,931	13,383			
20–24	68,598	24,535	47,581			
25–29	123,144	45,246	91,185			
30–34	139,628	50,348	100,270			
35+	99,243	36,000	71,034			
Total[c]	**450,806**	**163,072**	**323,507**			
		NTD rate[d]		*% diff*[e]	*RR*[f]	*RR 95%CI*[g]
<20	14.9	13.0	6.7	–54.8	0.45	0.215, 0.952
20–24	11.5	11.0	8.2	–28.8	0.71	0.485, 1.044
25–29	9.5	7.5	7.9	–16.9	0.83	0.620, 1.115
30–34	8.7	8.9	8.1	–6.8	0.93	0.704, 1.235
35+	7.6	9.2	9	19.2	1.19	0.854, 1.664
Total	**10.2**	**9.4**	**8.7**	**–14.4**	**0.86**	**0.738, 0.993**

Notes follow the final table in this section

Table F4: NTD rates among conceptions and change in NTD rates over time by maternal Indigenous status, NSW, Qld, WA, SA and NT

Maternal Indigenous status	Study periods[a] Baseline	Transition	Standard		Change in NTD rates	
			NTD-affected babies			
Aboriginal /Torres Strait Islander	42	11	8			
Non-Indigenous	399	136	260			
Missing data	18	6	14			
Total	**459**	**153**	**282**			
			Conceptions[b]			
Aboriginal or Torres Strait Islander origin	21,403	7,710	15,802			
Non-Indigenous	428,792	155,160	307,265			
Total[c]	**450,806**	**163,072**	**323,507**			
		NTD rate[d]		*% diff*[e]	*RR*[f]	*RR 95%CI*[g]
Aboriginal or Torres Strait Islander origin	19.6	14.3	5.1	–74.2	0.26	0.121, 0.549
Non-Indigenous	9.3	8.8	8.5	–9.1	0.91	0.778, 1.063
Total	**10.2**	**9.4**	**8.7**	**–14.4**	**0.86**	**0.738, 0.993**

Notes follow the final table in this section

Notes for tables F1 to F4

(a) Three study periods comprise a baseline period from October 2006 for New South Wales, Western Australia, South Australia and the Northern Territory, and April 2007 for Queensland to December 2008; a transition period from January 2009 to the end of September 2009, during which folic acid fortification of bread flour may have commenced in some places; and the period from October 2009 to March 2011, in which the mandatory fortification standard applied

(b) The number of conceptions in the study periods that resulted in a live birth or a stillbirth for residents of New South Wales, Queensland, Western Australia, South Australia and the Northern Territory. Unpublished aggregate data. **Source:** Australian Institute of Health and Welfare (AIHW) National Perinatal Data Collection. Details of the collection retrieved 25 February 2016 from http://www.aihw.gov.au/mothers-and-babies/

(c) Total conceptions in each period include those with missing data

(d) NTD rate per 10,000 conceptions in each period. that ended as a birth

(e) Per cent difference (% diff) is the NTD rate in the standard period minus the NTD rate in the baseline period divided by the NTD rate in the baseline period and expressed as a percentage.

(f) Relative rate (RR) is the NTD rate in the standard period relative to the NTD rate in the baseline period. Note that (1-RR)*100=%diff.

(g) Relative rate 95% confidence interval (RR 95%CI) that does not include 1 indicates that the RR (and %diff) is statistically significant.

Appendix G: Tabulated results, population omitting NSW

Table G1: NTD rates among conceptions and change in NTD rates over time by type of NTD, residents of Qld, WA, SA and NT

NTD type	Study periods[a]					
	Baseline	Transition	Standard			Change in NTD rates
			NTD-affected babies			
Anencephaly	144	41	95			
Spina bifida	123	55	88			
Encephalocoele	30	9	15			
NTD	297	105	198			
			Conceptions[b]			
	231,146	**88,823**	**176,203**			
		NTD rate[d]		***% diff[e]***	***RR[f]***	***RR 95%CI [g]***
Anencephaly	6.2	4.6	5.4	–13.5	0.87	0.677, 1.121
Spina bifida	5.3	6.2	5	–6.2	0.94	0.714 , 1.234
Encephalocoele	1.3	1.1	0.9	–34.4	0.66	0.353, 1.219
NTD	**12.8**	**11.8**	**11.2**	**–12.5**	**0.87**	**0.731, 1.047**

Notes follow the final table in this section

Table G2: NTD rates among conceptions and change in NTD rates over time for NTD classified by co-existent anomaly, residents of Qld, WA, SA and NT

Co-existent anomaly	Study periods[a]					
	Baseline	Transition	Standard			Change in NTD rates
			NTD-affected babies			
Isolated	248	83	163			
Non-Isolated	38	21	29			
Uncertain	11	1	6			
Total NTD	297	105	198			
			Conceptions[b]			
	231146	**88823**	**176203**			
			Per cent of total NTD			
Isolated	83.5	79.0	82.3			
Non-Isolated	12.8	20.0	14.6			
		NTD rate[d]		***% diff[e]***	***RR[f]***	***RR 95%CI[g]***
Isolated	10.7	9.3	9.3	-13.8	0.9	0.708 , 1.051
Non-Isolated	1.6	2.4	1.6	0.1	1.0	0.617, 1.623
NTD	**12.8**	**11.8**	**11.2**	**–12.5**	**0.87**	0.731 , 1.047

Notes follow the final table in this section

Table G3: Change in NTD rates among conceptions and change in NTD rates over time, by maternal age, residents of Qld, WA, SA and NT

Maternal age	Study periods[a] Baseline	Transition	Standard			Change in NTD rates
		NTD-affected babies				
<20	23	7	6			
20–24	56	21	31			
25–29	85	22	56			
30–34	81	30	53			
35+	52	25	52			
Missing data	0	0	0			
Total	**297**	**105**	**198**			
		Conceptions[b]				
<20	12,367	4,468	8,615			
20–24	38,801	14,651	28,498			
25–29	64,151	25,245	51,025			
30–34	68,530	26,469	52,384			
35+	47,291	17,989	35,679			
Total[c]	**231,146**	**88,823**	**176,203**			
		NTD rate[d]		***% diff[e]***	***RR[f]***	***RR 95%CI [g]***
<20	18.6	15.7	7	–62.6	0.37	0.153, 0.919
20–24	14.4	14.3	10.9	–24.6	0.75	0.486, 1.169
25–29	13.3	8.7	11	–17.2	0.83	0.591, 1.160
30–34	11.8	11.3	10.1	–14.4	0.86	0.606, 1.210
35+	11	13.9	14.6	32.6	1.33	0.903, 1.946
Total	**12.8**	**11.8**	**11.2**	**–12.5**	**0.87**	**0.731, 1.047**

Notes follow the final table in this section

Table G4: Change in NTD rates among conceptions and change in NTD rates over time, by Indigenous status, residents of Qld, WA, SA and NT

Indigenous status	Study periods[a] Baseline	Transition	Standard			Change in NTD rates
		NTD-affected babies				
Aboriginal or Torres Strait Islander origin	33	7	5			
Non-Indigenous	262	97	191			
Missing data	2	1	2			
Total	**297**	**105**	**198**			
		Conceptions[b]				
Aboriginal or Torres Strait Islander origin	14,484	5,373	11,057			
Non-Indigenous	216,558	83,412	165,086			
Total[c]	**231,146**	**88,823**	**176,203**			
		NTD rate[d]		***% diff[e]***	***RR[f]***	***RR 95%CI [g]***
Aboriginal or Torres Strait origin	22.8	13.0	4.5	–80.2	0.20	0.078, 0.508
Non-Indigenous	12.1	11.6	11.6	–4.4	0.87	0.731 , 1.006
Total	**12.8**	**11.8**	**11.2**	**-12.5**	**0.87**	**0.731, 1.047**

Notes follow the final table in this section

Table G5: Change in isolated NTD rates among conceptions and change in NTD rates over time by maternal age, Qld, WA, SA and NT

Maternal age	Study periods[a] Baseline	Transition	Standard	Change in NTD rates		
	Non-isolated NTD-affected babies					
<20	18	6	6			
20–24	49	16	23			
25–29	74	18	47			
30–34	68	24	47			
35+	36	14	31			
Missing data	0	0	0			
Total	248	83	163			
	Conceptions[b]					
<20	12,367	4,468	8,615			
20–24	38,801	14,651	28,498			
25–29	64,151	25,245	51,025			
30–34	68,530	26,469	52,384			
35+	47,291	17,989	35,679			
Total[c]	231,146	88,823	176,203			
	Isolated NTD rate[d]			***% diff[e]***	***RR[f]***	***RR 95%CI [g]***
<20	14.55	13.43	6.96	-52.1	0.479	0.190 , 1.205
20–24	12.63	10.92	8.07	-36.1	0.639	0.389 , 1.049
25–29	11.54	7.13	9.21	-20.1	0.799	0.554 , 1.150
30–34	9.92	9.07	8.97	-9.6	0.904	0.624 , 1.311
35+	7.61	7.78	8.69	14.1	1.141	0.706 , 1.845
Total	**10.73**	**9.34**	**9.25**	**-13.8**	**0.862**	**0.708 , 1.050**

Notes follow the final table in this section

Notes for tables G1 to G5

(a) Three study periods comprise a baseline period from October 2006 for Western Australia, South Australia and the Northern Territory, and April 2007 for Queensland to December 2008; a transition period from January 2009 to the end of September 2009, during which folic acid fortification of bread flour may have commenced in some places; and the period from October 2009 to March 2011, in which the mandatory fortification standard applied.

(b) The number of conceptions in the study periods that resulted in a live birth or a stillbirth for residents of Queensland, Western Australia, South Australia and the Northern Territory. Unpublished aggregate data. **Source:** Australian Institute of Health and Welfare (AIHW) National Perinatal Data Collection. Details of the collection retrieved 25 February 2016 from http://www.aihw.gov.au/mothers-and-babies/

(c) Total conceptions in each period include those with missing data.

(d) NTD rate per 10,000 conceptions in each period that ended as a birth.

(e) Per cent difference (% diff) is the NTD rate in the standard period minus the NTD rate in the baseline period divided by the NTD rate in the baseline period and expressed as a percentage.

(f) Relative rate (RR) is the NTD rate in the standard period relative to the NTD rate in the baseline period. Note that (1-RR)*100=%diff.

(g) Relative rate 95% confidence interval (RR 95%CI) that does not include 1 indicates that the RR (and %diff) is statistically significant.

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