

# Neural tube defects in the Republic of Ireland in 2009–11

R. McDonnell<sup>1</sup>, V. Delany<sup>1</sup>, M.T. O'Mahony<sup>2</sup>, C. Mullaney<sup>3</sup>, B. Lee<sup>4</sup>, M.J. Turner<sup>4</sup>

<sup>1</sup>Health Intelligence Unit, Health Service Executive, Dr Steevens Hospital, Dublin 8, Ireland

<sup>2</sup>Department of Public Health, Health Service Executive, Block 8, St Finbar's Hospital, Douglas Road, Cork, Ireland

<sup>3</sup>Department of Public Health, Health Service Executive, Lackan, Dublin Road, Kilkenny, Ireland

<sup>4</sup>UCD Centre for Human Reproduction, Coombe Women and Infants University Hospital, Cork Street, Dublin 8, Ireland

Address correspondence to Bob Mc Donnell, E-mail: bob.mcdonnell@hse.ie

## ABSTRACT

**BACKGROUND** Neural tube defects (NTDs) are associated with deficient maternal folic acid peri-conceptionally. In Ireland, there is no mandatory folic acid food fortification, partly due to declining NTD rates in recent years. The aim of this study was to ascertain the incident rate of NTD during the period 2009–11 and describe epidemiologically NTD in Ireland.

**METHODS** Cases were ascertained through multiple sources, including three regional congenital anomaly registers, all maternity hospitals nationally and paediatric hospitals providing care for children with spina bifida in the Republic of Ireland during the period 2009–11.

**RESULTS** From 225 998 total births, 236 NTDs were identified, giving an incidence of 1.04/1 000 births, increasing from 0.92/1 000 in 2009 to 1.17/1 000 in 2011. Of all cases, 45% ( $n = 106$ ) had anencephaly, 49% ( $n = 115$ ) had spina bifida and 6% ( $n = 15$ ) had an encephalocele; 78% ( $n = 184$ ) were liveborn or stillborn and 22% ( $n = 52$ ) were terminations abroad. Peri-conceptual folic acid supplement intake was 13.7% among the 52.5% ( $n = 124$ ) of cases whose folic acid supplement intake was known.

**CONCLUSION** The incidence of NTDs in the Republic of Ireland appears to be increasing. Renewed public health interventions, including mandatory folic acid food fortification, must be considered to reduce the incidence of NTD.

## Introduction

Neural tube defects (NTDs) are major congenital anomalies that have a profound impact on families and health services. The estimated total lifetime cost for each patient with spina bifida is more than half a million euros.<sup>1</sup> It is established that up to 70% of NTDs are preventable through adequate intake of folic acid by the woman peri-conceptionally.<sup>2</sup> In Ireland, three regional registries provide systematic surveillance of congenital anomalies covering 62% of births nationally. These EUROCAT registries, members of a European-wide network of >40 congenital anomaly registries in 23 countries,<sup>3</sup> operate in the east, southeast and south of Ireland. There is no monitoring of congenital anomalies, including NTDs, in the remaining areas of the country accounting for 38% of births.

From the early 1980s, NTD incidence rates in Ireland and the UK were substantially higher than other regions of Europe. Rates gradually declined.<sup>4,5</sup> Although the difference in NTD rates between Ireland and Europe narrowed by 2000, Ireland continued to have a higher rate than some other European

countries.<sup>6</sup> Irish studies in the late 1990s and early 2000s showed a low intake of peri-conceptual folic acid supplements by women of child-bearing age.<sup>7,8</sup> Ireland has no national NTD screening policy; routine screening for maternal serum alpha-fetoprotein is not undertaken. Individual clinicians may choose to undertake an ultrasound congenital anomaly scan ~20 weeks of gestation, usually in university teaching hospitals, though not in other maternity hospitals or units. Overall, ~61% of antenatal patients have an ultrasound congenital anomaly screening scan. A policy of mandatory folic acid fortification of staple foodstuffs was adopted by the Irish government

R. McDonnell, Consultant in Public Health Medicine

V. Delany, Research Nurse

M.T. O'Mahony, Consultant in Public Health Medicine

C. Mullaney, Consultant in Public Health Medicine

B. Lee, Programme Manager, Obstetrics and Gynaecology

M.J. Turner, Professor of Obstetrics and Gynaecology

in 2006,<sup>9,10</sup> an approach already in practice in USA<sup>11,12</sup> and >50 other countries worldwide.<sup>13</sup> However, its implementation was postponed when a baseline pre-fortification national study of NTD for the years 2005–06 found a lower incidence<sup>14</sup> compared with NTD data from the three regional EUROCAT registries for previous years. In Ireland, as in other European Union countries, economic austerity programmes associated with deteriorating socio-economic circumstances have decreased household spending on food,<sup>15</sup> with possible implications for intake of natural folate and consequently the rate of NTD. The objective of this study was to ascertain the incident rate of NTD and describe the epidemiological and clinical outcomes of NTD in Ireland during the period 2009–11.

## Methods

An NTD case was defined as one of the following: anencephaly, spina bifida or encephalocele. Cases of iniencephaly were grouped with anencephaly. Cases of lipomyelomeningocele and atretic encephalocele were excluded; though resembling NTD clinically, they are not considered as NTD or classified as such by the EUROCAT network.

The EUROCAT regional congenital anomaly registries in the east, south and southeast of the country provided anonymized data on NTD cases in their regions. The methods of EUROCAT registries are described elsewhere ([www.eurocat-network.eu](http://www.eurocat-network.eu)). The registry in the east gathered information on NTD cases in the remaining parts of the country where there is no congenital anomaly surveillance. Data on the numbers and type of NTD diagnosed were requested from all maternity hospitals. These data were gathered using a datasheet (one per case) with demographic, diagnostic, delivery, clinical outcome, obstetric and family history variables. Information on folic acid supplement intake was also requested, including the dose and when taken (pre-pregnancy/during pregnancy with gestation). In line with EUROCAT standards, multiple other sources of ascertainment of NTD cases were used; these included birth notification forms, post-mortem reports, maternity and paediatric hospital reports, the Hospital Inpatient Enquiry System, the National Perinatal Reporting System (NPRS), stillbirth and death registrations, as well as NTD diagnoses ascertained from cases receiving disability benefit. The examination of multiple sources means that enough information is available to assist in the ascertainment of an NTD case and enable cross-checking and confirmation with other data sources. Individual case records were reviewed to record socio-demographic and clinical details. Clinical information was also obtained from the National Paediatric Neurosurgical Centre (national centre for treatment of spina bifida). Members of the national support organization for those affected by NTD, Spina Bifida Hydrocephalus Ireland

([www.SBHL.ie](http://www.SBHL.ie)), also provided additional data for the study by encouraging their members to participate in the provision of information to the study.

Registration of all stillbirths is compulsory in Ireland. Data are kept in the Central Statistics Office that provided data on all stillbirths for the study period. As termination of pregnancy for congenital anomaly (TOPFA) is not legal; there is no official recording of information. In some cases, clinical records confirmed that the woman had obtained a termination abroad following prenatal diagnosis of NTD in Ireland. In other cases, the outcome of the pregnancy following prenatal diagnosis of NTD in Ireland was unknown, as these women did not subsequently give birth in the hospital where booked for antenatal care. The assumption was made that these women were likely to have obtained termination of pregnancy abroad. This assumption was made on the basis of consultation with clinicians. It was considered usual that births other than terminations would entail communication between clinicians in Ireland and the hospital of birth, considering the presence of a major congenital anomaly. For this study, we therefore defined a TOPFA as a case of NTD where the outcome of the pregnancy was known to be a termination confirmed by a clinician, or a prenatally diagnosed NTD case where the outcome was unknown but clinically very likely to have been a termination. Limited socio-demographic data and no delivery data were available for cases where the outcome was a TOPFA.

The denominator population was the number of live births and stillbirths nationally in Ireland for each of the 3 years, as reported by the NPRS.<sup>16</sup> During the 3 years there were 225 998 births in the Republic of Ireland. The number of births (live births + stillbirths) in each of the 3 years was: 76 021 births in 2009, 75 600 in 2010 and 74 377 in 2011. Approximately 24% of births each year during the years 2009–11 were to women born outside Ireland. Many of these women had arrived in Ireland within the previous 10 years and may have had a different risk profile for NTD compared with Irish-born mothers. The total births to Irish mothers during the 3-year period was 171 451, the total births to non-Irish mothers was 54 547.

## Statistical analysis

NTD incident rates per 1000 births were examined for the 3 years. The following variables were compared by type of NTD: incidence, type of birth outcome (live birth, stillbirth, TOPFA) and proportions prenatally diagnosed. Incident rates were calculated by nationality, comparing Irish with non-Irish mothers. Incident rates were also calculated for eight regions within the country (the capital—Dublin, mid-east, mid-west,

**Table 1** Neural tube defect numbers and rate per 1000 births by type and year.

	Anencephaly, n (%), rate	Spina bifida, n (%), rate	Encephalocoele, n (%), rate	Total, n, rate
2009	30 (42.9), 0.39	37 (52.9), 0.49	3 (4.3), 0.04	70, 0.92
2010	43 (54.4), 0.57	31 (39.2), 0.41	5 (6.3), 0.07	79, 1.04
2011	33 (37.9), 0.44	47 (54.0), 0.63	7 (8.0), 0.09	87, 1.17
Total	106 (44.9), 0.47	115 (48.7), 0.51	15 (6.4), 0.07	236, 1.04

**Table 2** Type of neural tube defect by pregnancy outcome.

	Anencephaly, n (%)	Spina bifida, n (%)	Encephalocoele, n (%)	Total, n (%)
Live birth	41 (61.2)	94 (88.7)	10 (90.9)	145 (78.8)
Stillbirth	26 (38.8)	12 (11.3)	1 (9.1)	39 (21.2)
Total	67 (100.0)	106 (100.0)	11 (100.0)	184 (100.0)

southeast, southwest, border region, midland, west). The data were analysed on EPI Info software.<sup>17</sup> The  $\chi^2$  test was used for comparison of proportions.

## Results

During the 3-year period, there were 236 cases of NTD identified giving an overall incidence of 1.04/1000 births. The incidence rose from 0.92/1000 in 2009 to 1.04 in 2010 and 1.17/1000 in 2011, though this increase was not statistically significant. Of the cases, 44.9% ( $n = 106$ ) were diagnosed with anencephaly, 48.7% ( $n = 115$ ) with spina bifida and 6.4% ( $n = 15$ ) with an encephalocoele. Nationality was available for 231 (98%) of women; of these, 190 NTDs were born to Irish women, giving a rate of 1.11/1000 compared with a rate of 0.75/1000 for the 41 women of other nationalities ( $\chi^2 = 5.0$ ,  $df = 1$ ,  $P < 0.05$ ).

Table 1 shows the number and rate of all NTD by year. The main reason for the increase between 2009 and 2011 was a rise in the number of cases of spina bifida. Of the total 236 cases, 78% (184) were live births or stillbirths. Table 2 shows the number and proportions of each by type of NTD. The remaining 52 (22%) of NTD cases were a TOPFA, according to our definition; 39 were anencephaly diagnoses, 9 were spina bifida and 4 were encephalocoele, accounting for 36.8, 7.8 and 26.7% of total anencephaly, spina bifida and encephalocoele cases, respectively. Table 3 shows the number of NTD

**Table 3** Numbers and rate per 1000 births of NTD by type and age group of mother

	Anencephaly, n (rate)	Spina Bifida, n (rate)	Encephalocoele, n (rate)	All NTD, n (rate)
15–19	1 (0.17)	5 (0.83)	0 (0.00)	6 (1.0)
20–24	12 (0.49)	17 (0.69)	2 (0.08)	31 (1.27)
25–29	24 (0.45)	25 (0.47)	2 (0.04)	51 (0.96)
30–34	39 (0.50)	25 (0.32)	7 (0.09)	71 (0.90)
35–39	21 (0.40)	38 (0.72)	3 (0.06)	62 (1.17)
40+	9 (0.81)	5 (0.45)	1 (0.09)	15 (1.36)
Total	106 (0.47)	115 (0.51)	15 (0.07)	236 (1.04)

**Table 4** Gestational age at diagnosis of NTD—live births and stillbirths

	Anencephaly, n (%)	Spina bifida, n (%)	Encephalocoele, n (%)	Total, n (%)
< 16 weeks	50 (54.9)	6 (8.1)	3 (30.0)	59 (33.7)
16–19 weeks	11 (12.1)	10 (13.5)	3 (30.0)	24 (13.7)
20–23 weeks	22 (24.2)	30 (40.6)	1 (10.0)	49 (28.0)
24–38 weeks	8 (8.8)	28 (37.8)	3 (30.0)	43 (24.6)
Total	91	74	10	175

Note: Gestational age at diagnosis was unknown for 20 cases: anencephaly (8), spina bifida (11), encephalocoele (1).

analysed by the woman's age group. Those aged 20–24 and mothers aged 35 or more had higher rates, though not statistically significant.

Almost 83% ( $n = 195$ ) of NTDs were diagnosed prenatally, of whom the exact time of diagnosis was known for 175 cases, their gestation at diagnosis is shown in Table 4.

Of the 106 cases of anencephaly, 93.4% ( $n = 99$ ) were diagnosed prenatally, 24.5% ( $n = 26$ ) resulted in a stillbirth, 38.7% ( $n = 41$ ) were live births and 36.8% ( $n = 39$ ) were a TOPFA; 15 (14.2%) were delivered by Caesarean section. For the 115 cases of spina bifida, 73.9% ( $n = 85$ ) were diagnosed prenatally, 81.7% ( $n = 94$ ) were a live birth, 10.4% ( $n = 12$ ) were stillbirths and 7.8% ( $n = 9$ ) were a TOPFA; 50 (43.4%) were delivered by Caesarean section. Nine (9.6%) of the 94 spina bifida live births died in the neonatal period, 4 of whom had trisomy 13 or 18. The majority of live birth cases with spina bifida, 85 (90.4%), survived the neonatal period. Approximately 73 ( $n = 11$ ) of the 115 encephalocoele cases were diagnosed prenatally, 66.7% ( $n = 10$ ) were live births,

6.7% ( $n = 1$ ) were stillbirths and 26.7% ( $n = 4$ ) were a TOPFA; 5 (33.3%) were delivered by Caesarean section.

Just over 11% of the liveborn and stillborn NTD cases had at least one additional congenital anomaly ( $n = 21$ ). Eight of these had a chromosomal trisomy (e.g. trisomies 13 or 18) and four had major abdominal wall defects or diaphragmatic hernia. The remaining cases had a variety of other major or minor anomalies.

Information on folic acid supplements taken in the peri-conceptional period and during pregnancy was incomplete, with no information in 47.5% ( $n = 112$ ) of cases. The use of supplements by women for whom data were available ( $n = 124$ ) showed that 14.5% ( $n = 18$ ) had not taken supplements at any stage, 13.7% ( $n = 17$ ) had taken them pre-conceptionally, while 49.2% ( $n = 61$ ) took supplements post-conceptionally. Information on infertility treatment was available for 76.7% ( $n = 181$ ) of cases. Of these, 93.9% ( $n = 170$ ) had no infertility treatment and 6.1% ( $n = 11$ ) had infertility treatment. Of the latter, 27.3% ( $n = 3$ ) had not taken pre-conceptional folic acid supplements.

Eighteen (7.6%) of the 236 NTD cases were twin pregnancies. Of the 18 twin cases, 61% ( $n = 11$ ) had anencephaly, 28% ( $n = 5$ ) had spina bifida and 11% ( $n = 2$ ) had encephalocele.

There was no pregnancy in which both twins were affected. The overall rate of NTDs per 1000 for twin births was higher than the NTD rate for singleton births (2.4 versus 1.0;  $\chi^2 = 13.7$ ,  $df = 1$ ,  $P < 0.001$ ). The rate for anencephalic twin births was also higher than that for singleton births (1.5 versus 0.4;  $\chi^2 = 16.5$ ,  $df = 1$ ,  $P < 0.001$ ). The rate per 1000 births for spina bifida did not differ between singleton and multiple births.

Overall, 3.4% ( $n = 8$ ) of women reported having a previous pregnancy affected with a congenital anomaly. Of the eight previously affected pregnancies, one was a case of anencephaly, two were chromosomal trisomies, one was an abdominal wall defect and one was a diaphragmatic hernia; the remaining three were minor anomalies. Of the total 236 women, 2.5% ( $n = 6$ ) had either first- or second-degree relatives with a confirmed or suspected history of NTD.

Regionally, the incidence of NTDs per 1000 births was as follows: Dublin (0.76), mid-east (1.06), mid-west (1.09), southeast (1.25), southwest (0.95), border (1.34), midlands (1.46) and west (1.09).

Figure 1 shows the rates of NTD in Ireland and Europe (excluding the UK as it shares a similar NTD risk with Ireland) for the years 2000–11. The NTD rates of this study (2009–11) and the previous study (2005–06)<sup>14</sup> are included, with an estimate of the rate in years 2007–08 based on data from the combined Irish EUROCAT registries and including a similar TOPFA proportion as the study years. The data for

all other years are those of the combined Irish EUROCAT registries, with the coverage of 62% of births nationally.

## DISCUSSION

### Main findings

We observed a rise in NTD rates in successive years from 2009 to 2011 in the Republic of Ireland, in contrast to previous reports of declining rates. The overall rate at 1.04 per 1000 births during the 3-year period was also higher than observed in the previous decade.<sup>18</sup> The rate of NTDs was significantly higher among Irish mothers compared with non-Irish mothers, confirming the historic higher risk of Irish mothers of having an NTD-affected pregnancy, in part related to MTHFR polymorphism.<sup>19</sup>

The outcome for the majority of affected pregnancies was a stillbirth or TOPFA with regard to anencephaly, whereas most spina bifida cases were liveborn. More than 90% of NTDs were diagnosed prenatally, with three-quarters being diagnosed before 24 weeks of gestation. This is comparable to prenatal detection rates elsewhere in Europe.<sup>20,21</sup>

Our study suggested that the rate of NTDs may be lower in the Dublin region than the rest of the country. It is possible that socio-economic differences on food expenditure in households may explain the disparity as Dublin households have up to 20% more disposable income on average compared with other regions.<sup>15</sup> We observed higher rates of NTDs and anencephaly in twins compared with singleton births; this has also been reported in other studies,<sup>22,23</sup> though our observed rates are higher than those of previous studies. Information on folic acid supplementation use was seriously incomplete, but what was available suggested a very low uptake pre-conceptionally at 13.7%, and concurs with similar evidence from previous studies of folic acid supplementation use in Ireland.<sup>24,25</sup>

### What is already known on the topic

In Ireland and the UK, there has been a long history of high NTD rates, with declining rates in the 1980s and 1990s. A previous study published only as part of a report<sup>14</sup> on the incidence rate of NTD in Ireland, undertaken in 2005–06, was limited by the use of primarily one method of ascertainment and fewer socio-demographic variables and covered a study period of <2 years. The incidence rate of NTD in that study was 0.93 per 1000 births, lower than the rates in our study.

Rates of NTDs are monitored in Europe through the EUROCAT network of congenital anomaly registries. However, other than some Scandinavian countries and Poland, most European registries are regional, providing population-based surveillance within defined geographical areas, rather than



**Fig. 1** NTD per 1000 births in Ireland and Europe 2000–11. Note: Europe rate exclude UK and Ireland. Rates for 2000–04 are Irish EUROCAT registry data rates (62% national coverage); 2009–11 rates are from this study, rates from 2005–06 are from the previous study, rates for years 2007–08 are estimated. Data on Europe rates from EUROCAT network.

national country-wide surveillance. Therefore, few countries have national data on NTD. In Europe, the overall rate of NTDs, as represented by the combined registries of the EUROCAT network (which includes the three Irish EUROCAT registries) has remained fairly constant between 0.96 and 0.98 per 1000 births throughout the last decade, lower than the rate in our study. The European rate for spina bifida is similar to our study for the same time period (0.51 per 1000 births for Ireland in our study, 0.49 in Europe). The anencephaly rate for Ireland in our study was higher than in Europe (0.47 versus 0.36), though the rate for encephalocele was lower (0.07 versus 0.15).<sup>18</sup> It is important to note that within Europe, there is heterogeneity with some regional registries having higher rates and others with lower rates than Ireland. Comparison with countries outside of Europe is inappropriate as many have lower rates of NTD following the introduction of mandatory fortification of staple foodstuffs with folic acid, e.g. North and South America, Middle East, Africa and Australia, with reported lower rates of NTDs after fortification was introduced.<sup>26–29</sup>

### What this study adds

Our study provides the most up-to-date and accurate data on the incidence of NTD at a national level in the Republic of Ireland; the multiple methods of ascertainment we used were comprehensive, including data from the three regional EUROCAT registries and from all maternity units in the

country. National data on NTD are lacking in Europe, regional rates allow only for estimates of national incidence, which may not always be appropriate due to differences in rates within regions of the same country. Though baseline data gathered previously<sup>14</sup> in preparation for folic acid fortification (subsequently postponed in 2008) indicated a high level of voluntary folic acid fortification by food producers and also high intake of such foods by women in Ireland, no similar information on the intake of fortified foods by women of child-bearing age is available since the severe economic downturn in 2009. Notwithstanding this, the findings of the study will serve as a basis on which to review the issue of folic acid fortification. Our study also provides information on the outcome of NTD-affected pregnancies that was previously unclear, firstly, showing that the majority of NTD-affected births are liveborn, having important implications for families and health service provision particularly in relation to spina bifida, and secondly, that in almost a quarter of cases the outcome was a TOPFA, notwithstanding that it is not legal in Ireland.

### Limitations of study

A limitation of this study was the absence of data for some demographic and lifestyle variables, particularly in cases where the outcome was a TOPFA. Information on two important risk factors, folic acid supplementation and body mass index was very incomplete. It is possible that some



cases of NTDs may have been missed following diagnoses made in private clinics that subsequently had a TOPFA outcome, though we estimate that this number is negligible, as almost all privately diagnosed cases of NTDs are referred to the main maternity hospitals for confirmation of diagnosis. It is also possible that some terminations of pregnancy for chromosomal trisomies may have included cases that also had an NTD as an additional anomaly which would not have been diagnosed if the primary reason for the TOPFA was the chromosomal anomaly. Although likely to be a very small proportion, they would not have been ascertained in our study.

## Conclusion

The decline in the rate of NTDs in Ireland appears to be changing and possibly reversing. This will have important consequences for individuals born with an NTD, their families and health services. The rise in NTD rates is in the indigenous Irish rather than among immigrant mothers. In Ireland, unlike most other countries in Europe, the vast majority of spina bifida cases are liveborn. Individuals with NTD and their families pay the personal cost of this largely preventable congenital anomaly. In economic terms it involves a consequent financial burden on an already overstretched health service. We believe that the results of our national study provide grounds for an urgent review of public health policy on folic acid fortification, folic acid supplementation and pre-conceptional care in Ireland in the primary prevention of NTD.

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