Neural Tube Defects in Malaysia: Data from the Malaysian National Neonatal Registry

by Nem-Yun Boo,1 Irene G. S. Cheah,2 Meow-Keong Thong,3 and for Malaysian National Neonatal Registry
1Faculty of Medicine and Health Sciences, Universiti Tunku Abdul Rahman, 43000 Kajang, Selangor, Malaysia
2Department of Paediatrics, Paediatric Institute, Hospital Kuala Lumpur, 50586 Kuala Lumpur, Malaysia
3Department of Paediatrics, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

Correspondence: Nem-Yun Boo, Faculty of Medicine and Health Sciences, Universiti Tunku Abdul Rahman, Jalan Sungai Long, Bandar Sungai Long, 43000 Kajang, Selangor, Malaysia. Tel: +603-9019-4722. Fax: +603-9019-1959.
E-mail <boony@utar.edu.my>; <nemyun_boo@yahoo.com>.

Summary
This study aimed to determine the prevalence and early outcome of neural tube defects (NTDs) in Malaysia. This prospective study included all neonates with NTDs (spina bifida, anencephaly, encephalocele) born in 2009 in 32 Malaysian hospitals in the Malaysian National Neonatal Network. The prevalence of NTDs was 0.42 per 1000 live births, being highest among the indigenous people of Sarawak (1.09 per 1000 live births) and lowest among Malaysians of Chinese descent (0.09 per 1000 live births). The most common type of NTDs was anencephaly (0.19 per 1000 live births), followed by spina bifida (0.11 per 1000 live births) and encephalocele (0.07 per 1000 live births). Majority of the infants with anencephaly (94.5%, n = 51), 45.8% (n = 11) with encephalocele and 9.5% (n = 4) with spina bifida died. The median duration of hospital stay was 4 (range: 0–161) days.

Conclusion: NTDs were common in Malaysia. Mortality was high. Long-term monitoring of NTD prevalence following folic fortification of food is recommended.

Key words: neural tube defects, Malaysia.

Acknowledgements
The authors would like to thank the Director General of the Ministry of Health of Malaysia for giving them the permission to publish this paper. The authors would also like to thank and acknowledge the members of the Malaysian National Neonatal Registry (MNNR) who have contributed to the data in this paper. The following were members of the 2008/2009 Steering Committee of the Malaysian National Neonatal Registry: Dr Irene Guat-Sim Cheah (Chairperson), Dr Jimmy Kok-Foo Lee, Dr Thian-Lian Soo, Prof. Dr Hans van Rostenbergh, Professor Dr Meow-Keong Thong, Dr Anna Padma Soosai, Dr Alvin Shang-Ming Chang and Professor Dr Nem-Yun Boo.

The following were site coordinators of the participating hospitals: Dr Keng-Hwang Teh (Hospital Sultanah Bahiyah), Dr Ahmad Amin (Batu Pahat Hospital), Dr Nor Azlina bt Mohd Rashid (Hospital Raja Permaisuri Bainun, Ipoh), Dr Min-Hong Soo (Kajang Hospital), Dr Ang Siang Shie and Dr Thant-Sin Khin (Keningau Hospital), Dr Irene Guat-Sim Cheah & Dr Soek-Chiong Chee (Kuala Lumpur Hospital), Dr Thian-Lian Soo (Sabah Women and Children Hospital), Dr Leow Poy Lee (Melaka Hospital), Dr Norfawwati Faridatul Akma (Miri Hospital), Dr Revathy Nallusamy (Pulau Pinang Hospital), Dr Fazila Mohd Kuttu (Putrajaya Hospital), Dr Hasmawati bt Hasan (Raja Perempuan Zainab II Hospital, Kota Bharu), Dr Lee-Gaik Chin (Sarawak General Hospital), Dr Angeline Yeoh (Seberang Jaya Hospital), Dr Rohaijah Borhan (Serdang Hospital), Dr Boo-Aik Khoo (Selayang Hospital), Dr Sow-Keng Chan (Ser Manjung Hospital), Dr Audrey Chae-Hee Chieng (Sibu Hospital), Dr Rohani bt. Abdul Jalili (Sultan Haji Ahmad Shah Hospital, Temerloh), Dr Angelina Seng-Lian Wan (Sultanah Aminah Hospital, Johor Bahru), Dr Pui-Ying Tham (Sultanah Fatimah Specialist Hospital, Muar), Dr Jimmy Kok-Foo Lee and Dr Sharifah Huda bt Engku Alwi (Sultanah Nur Zaharah Hospital, Kuala Terengganu), Dr Chong-Ming Choo and Dr Khairul Idzwan (Sungai Petani Hospital), Dr Ismail Haron (Sungai Buloh Hospital), Dr Siew-Hong Neo (Taiping Hospital), Dr Su-Yuen Ng (Teluk Intan Hospital), Dr Choy-Nyok Chin (Tengku Ampuan Afzan Hospital, Kuantan), Dr Yogeswary Sithaparanathan and Dr Padma Soosai (Tengku Ampuan Rahimah Hospital, Klang), Dr Jamaluddin b Mohammad (Tuanku Fauziaw Hospital, Kangar), Dr Umatheri Paramasivam (Tuanu Jafar Hospital, Seremban), Prof. Dr Hans van Rostenbergh and Dr Noraida Ramli (Universiti Sains Malaysia Hospital).

N.Y.B. designed, analysed and interpreted the statistical analysis, and prepared the manuscript. I.G.S.C. designed the survey, coordinated the gathering of data and reviewed the manuscript. M.K.T. designed the survey and reviewed the manuscript.

Funding
Clinical Research Centre, Ministry of Health and the Perinatal Society of Malaysia.
Introduction

In recent years, the prevalence of neural tube defects (NTDs) has declined markedly in many countries, from 1 per 1000 birth to 0.1–0.3 per 1000 births [1–5]. Besides early pregnancy screening programme coupled with induced abortion of abnormal foetuses, periconceptional folic acid supplementation has reduced the incidence of NTDs [3–10]. However, as not all women take or have access to periconceptional folic acid supplementation, the prevalence in some countries could not be reduced to a greater extent as expected. Consequently, mandatory food (flour in particular) fortification with folic acid has been widely proposed or implemented in many countries in recent years to reduce the prevalence of NTDs further [3–10].

In Malaysia, consumption of wheat-based products, especially noodles, is very popular in all segments of the society. However, mandatory food fortification with folic acid has not been implemented, although preparation is underway by the government to implement this in the near future. Voluntary food fortification is encouraged and practiced by some manufacturers. A study on folate intake by Malaysian women of childbearing age showed that 15.1% of the women had plasma folate deficiency (<6.8 nmol/L), and 84.8% had red blood cell folate levels below 906 nmol/L, indicating inadequate blood folate for protection from NTDs in pregnancy [11].

The prevalence of NTDs is unknown in Malaysia, as no large-scale population study has been undertaken. A smaller population-based survey in the Kinta district of Malaysia in 2001–2002 reported a birth prevalence of NTDs of 0.73 per 1000 live births in 17720 live births [12]. The Malaysian National Neonatal Registry (MNNR) has member neonatal intensive care units from 32 out of 40 public hospitals in Malaysia. These member hospitals delivered more than half of the annual total live births in the country. Therapeutic termination of pregnancy is only legally allowed for maternal indications in this country and not routinely performed in public hospitals. In view of this, the prevalence of NTDs from these hospitals under MNNR may give an estimate of the extent of NTDs in Malaysia.

This study aimed to determine the baseline prevalence of NTDs in the MNNR and early outcome of this group of infants before implementation of mandatory folic acid fortification programme (FFP). The baseline data may help us to gauge the impact of the FFP when implemented in the near future.

Methods

This was a prospective cohort study. Neonates born in the year 2009 and diagnosed to have NTDs in 32 out of the 40 Malaysian public hospitals participating in the MNNR were included in the study.

The remaining six hospitals did not participate because they were small hospitals with few neonatal beds (six or less) and without pediatricians in 2009.

The following conditions were included as NTDs in this study: spina bifida (a defect in the vertebral column with corresponding spinal cord and meninges protruding with or without cover by the overlying skin), anencephaly (total or partial absence of the cranial vault and scalp, often with associated absence or reduction of brain tissues), encephalocoele ( herniation of the brain and/or meninges through a defect in the skull) or miscellaneous types of NTDs (such as tethered cord, lipomyelomeningocele and lipomeningocoele) based on the International Classification of Disease, 10th edition [13]. The demographic data of each of these infants (including their maternal age, ethnic groups, gravid status, parity, maternal illness during pregnancy, birth weight, gestational age and gender), types of NTDs, duration of hospital stay and outcome before discharge were entered into a standard format of the MNNR. Data on total live births of each of the participating hospitals were obtained from their respective hospital annual census.

The prevalence of NTDs among all inborn infants, each of the ethnic group of the inborn infants and each of the common types of NTDs among the inborn infants were calculated against the denominators of total live births in the hospitals participating.

Results

During the study period, there were 263034 live births in the MNNR. One hundred forty-one infants were admitted with NTDs, all with complete data. The mean maternal age of infants with NTDs was 28.5 years (95% CI: 27.4–29.5), median maternal gravid status was 2 (range: 1–3) and median parity was 1 (range: 0–11). Diabetes mellitus was present in 17% of these mothers and hypertension during pregnancy, birth weight, gestational age and gender), types of NTDs, duration of hospital stay and outcome before discharge were entered into a standard format of the MNNR. Data on total live births of each of the participating hospitals were obtained from their respective hospital annual census.

The prevalence of NTDs among all inborn infants, each of the ethnic group of the inborn infants and each of the common types of NTDs among the inborn infants were calculated against the denominators of total live births in the hospitals participating.
(2.1%) infants had Down syndrome, and two (1.4%) had Patau syndrome. Sub-group analysis showed that 53.7% of infants with anencephaly, 38.1% of infants with spina bifida, 61.9% of infants with encephalocoele and 50% of infants with miscellaneous types of NTDs were male. Seventy-two infants (51.1%) died before discharge. Thirty-three infants (45.8%) died before 12 h of life, and majority (75.8%, n = 25) had anencephaly. Majority of the infants with anencephaly (94.5%, n = 51), 45.8% (n = 11) of those with encephalocoele and 9.5% (n = 4) of those with spina bifida died before discharge. The median duration of hospital stay for all infants with NTDs was 4 (range: 0–161) days, for those with anencephaly was 1 (range: 0–161) day and for those with other types of NTDs was 10 (range: 0–128) days.

Majority (78%, n = 110) of the infants were inborn. The prevalence of NTDs was 0.42 per 1000 live births (Table 2). The highest prevalence was among the indigenous people of Sarawak, and the lowest among Malaysians of Chinese descent. There were 51, 28 and 18 inborn infants with anencephaly, spina bifida and encephalocoele, respectively. Thus, the prevalence of anencephaly was 0.19 per 1000 live births, spina bifida was 0.11 per 1000 live births and encephalocoele was 0.07 per 1000 live births.

**Discussion**

This study shows that the prevalence of NTDs in Malaysia was 0.42 per 1000 live births. Most of the infants with NTDs were born at term. Both genders

---

### Table 1

<table>
<thead>
<tr>
<th>Types of neural tube defects</th>
<th>Total no. of infants (%)</th>
<th>No. of infants in each ethnic group</th>
<th>No. of infants died before discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anencephaly only</td>
<td>53 (37.9)</td>
<td>M 32 C 1 I 1 SW 6 SB 3 F 9 O 1</td>
<td>50</td>
</tr>
<tr>
<td>Anencephaly with encephalocoele</td>
<td>1 (0.7)</td>
<td>M 1 C 0 I 0 SW 0 SB 0 F 0 O 0</td>
<td>1</td>
</tr>
<tr>
<td>Spina bifida only</td>
<td>36 (25.5)</td>
<td>M 25 C 2 I 4 SW 4 SB 0 F 1 O 0</td>
<td>4</td>
</tr>
<tr>
<td>Spina bifida with encephalocoele</td>
<td>2 (1.4)</td>
<td>M 1 C 0 I 0 SW 1 SB 0 F 0 O 0</td>
<td>0</td>
</tr>
<tr>
<td>Spina bifida and other miscellaneous types of neural tube defects</td>
<td>4 (2.8)</td>
<td>M 4 C 0 I 0 SW 0 SB 0 F 0 O 0</td>
<td>0</td>
</tr>
<tr>
<td>Encephalocoele only</td>
<td>20 (14.2)</td>
<td>M 11 C 0 I 2 SW 2 SB 2 F 3 O 0</td>
<td>10</td>
</tr>
<tr>
<td>Encephalocoele and other miscellaneous neural tube defects</td>
<td>1 (0.7)</td>
<td>M 0 C 1 I 0 SW 0 SB 0 F 0 O 0</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous types of neural tube defects</td>
<td>24 (17.0)</td>
<td>M 13 C 1 I 5 SW 1 SB 2 F 1 O 1</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>141</td>
<td>M 87 C 5 I 12 SW 14 SB 14 F 2 O 2</td>
<td>72</td>
</tr>
</tbody>
</table>

M, Malay; C, Chinese; I, Indian; SW, Sarawak indigenous people; SB, Sabah indigenous people; F, Foreigners; O, Malaysians of other ethnic groups.

### Table 2

<table>
<thead>
<tr>
<th>Ethnic groups of inborn infants</th>
<th>No. of inborn infants with neural tube defects</th>
<th>Total no. of live births</th>
<th>Prevalence per 1000 live births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malay</td>
<td>69</td>
<td>179484</td>
<td>0.38</td>
</tr>
<tr>
<td>Chinese</td>
<td>2</td>
<td>21848</td>
<td>0.09</td>
</tr>
<tr>
<td>Indian</td>
<td>8</td>
<td>14942</td>
<td>0.54</td>
</tr>
<tr>
<td>Sarawak indigenous people</td>
<td>11</td>
<td>10733</td>
<td>1.02</td>
</tr>
<tr>
<td>Sabah indigenous people</td>
<td>7</td>
<td>12626</td>
<td>0.55</td>
</tr>
<tr>
<td>Foreigners</td>
<td>11</td>
<td>17309</td>
<td>0.64</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>6092</td>
<td>0.33</td>
</tr>
<tr>
<td>Total</td>
<td>110</td>
<td>263034</td>
<td>0.42</td>
</tr>
</tbody>
</table>
were affected. Their mothers were generally young. Different ethnic groups had different prevalence, being highest among the Sarawak indigenous people and lowest among the Chinese. The most common type of NTDs in this cohort was anencephaly (38.3%), followed by spina bifida (29.8%), encephalocele (17.6%) and other miscellaneous NTDs (17.5%). This differed from findings from USA (South Carolina) and UK, where anencephaly accounted for 40.2 and 43.1%, spina bifida accounted for 44.3 and 50.5% and encephalocele accounted for 3.1 and 6.3%, respectively [14, 15]. The mortality rates of anencephaly and encephalocele were, however, similarly high, and death generally occurred during the first few days of life. The majority (>90%) of our infants with spina bifida survived to go home.

Our cohort of 141 infants with NTDs from various ethnic groups was the largest ever reported in Malaysia. The strength of our study lies in the large number of live births involved, and data came from the whole of Malaysia. The main limitations include the following: (i) failure to include NTDs in stillbirths and abortus in the participating hospitals, with resultant possible underestimation of the actual prevalence; (ii) lack of data from home deliveries (~5% of the total births) and from private hospitals; and (iii) screening of all the inborn infants, using ultrasonography, to detect spina bifida occulta and other less obvious NTDs such as tethered cord not being a routine in the participating centers. As a consequence, it is highly likely that we underestimated the actual prevalence of NTDs in Malaysia. Compared with an earlier small study in the district of Kinta in Malaysia [12], where the prevalence was reported to be 0.73 per 1000 live births, the prevalence detected in the present study (0.42 per 1000 live births) was much lower. The Kinta study included data on all live births with >22 weeks of gestation, all deliveries that occurred in both private and public hospitals and termination of pregnancies. However, the number of live births recruited was small, and only 13 infants were detected to have NTDs. Other reason for the lower prevalence of NTDs found in our study than the Kinta study could be recent improvements in dietary intake of folic acid or folate among Malaysians, and increased rates of termination of pregnancy for NTDs before 22 weeks of gestation.

Despite this underestimation, the prevalence of NTDs in the present study was still higher than that reported in the USA in the early 1990s before the implementation of food fortification with folic acid (0.378 per 1000 live births) [5]. Furthermore, even though our prevalence was similar to that reported by the Australians in 2005 (0.46 per 1000 births) [4], our prevalence could be underestimated, as we did not study NTDs in the stillbirths and terminations after 20 weeks as the Australians had done.

Similar to the Australian findings [4], younger mothers and indigenous women in Malaysia showed higher rates of having NTD infants. Without more detailed data, it is not clear why the Sarawakian indigenous people had higher prevalence than other Malaysians. Some possible reasons include (a) genetic predisposition [16]; (b) being a more rural community with less access to early antenatal care and information, periconceptional folic acid fortification and early antenatal diagnosis and termination of affected pregnancies; and (c) diet preference, with less exposure to food fortified with folic acid. Currently, folic acid fortification of food was voluntary and not mandatory in Malaysia. The urbanites, which constituted the majority of the Chinese Malaysian and large proportion of the Malays, had more access to such fortified food than communities living in very rural areas of Sarawak, where the road systems were less well developed. Although high rates of consanguinity were reported as an important cause of NTDs in some communities in other countries [16, 17], it is not likely a major cause of NTDs among the Sarawakian indigenous people, as consanguineous marriage was not encouraged and practiced commonly. In the present study, there were only a few infants with trisomies, suggesting that this was not a common risk factor associated with NTDs in the Malaysian cohort. Without data on maternal obesity and diabetes mellitus status of normal infants in our study, it is not possible to determine whether these were significant factors associated with NTDs in our cohort as reported by others [18, 19].

Based on the results of the present study and those of Khor et al. [11], which reported low serum levels of folic acid among Malaysian women in the childbearing age, there is an urgent need to actively promote periconceptional folic acid supplementation and consumption of local food rich in folic acid [20] among women of childbearing age in Malaysia, especially in Sarawak. Inclusion of information on the importance of folic acid consumption in the curriculum of health personnel and school children, public education and stepping up promotion of early antenatal care and antenatal screening are some of the strategies that need to be considered. Given the fact that there are some limitations in the extent to which periconceptional folic acid supplementation could reduce the prevalence of NTDs [3, 4], as not all women have access to or are willing to take folic acid supplementation, mandatory folic acid fortification of food should be implemented without further delay. Future studies on NTDs in Malaysia should include serial monitoring of trend of NTDs in different communities, investigation of serum and red blood cell folic acid level in the NTDs and normal population and epidemiological studies on risk factors of NTDs, and should aim to determine whether the types of
NTDs differ from Caucasian and other Asian populations.

References