Bayesian Small Area Cluster Analysis of Neural Tube Defects in Newfoundland

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ABSTRACT

Background: The incidence of neural tube defects (NTDs) is declining worldwide due to the implementation of folic acid supplementation programs. Such a program was implemented over 1996-97 in Newfoundland and Labrador, Canada. The geographical distribution of birth incidence was studied prior to and after the implementation of the program to identify regions of residual high incidence. Excess residual cases may potentially be due to genetic causes or incomplete supplementation program implementation.

Methods: Maternal place of residence for all provincial live birth and stillbirth notifications, provincial maternal-fetal medicine referrals, provincial rehabilitation referrals, and all provincial hospitals with NTDs or terminations for NTDs was obtained from 1975 to 2002 for near complete case ascertainment. Bayesian small area analysis was separately performed on cases from 1975-1996 and 1997-2002. The two time periods were compared.

Results: Birth incidence of NTDs was noted to decline after 1996, from 5.54/1000 live births to 1.08/1000 live births. 592 cases were found from 1975-1996 and 34 cases from 1997-2002. Relative risk of birth incidence was 0.93-1.18 (95% CI) for 1975-1996 and 0.97-1.02 for 1997-2002 after Bayesian smoothing. One region had an excess of residual cases greater than 34%.

Conclusions: The implications of this observation to the management of the public health initiative imply that overall response to the decrease in cases tends to be uniform across the province, with potentially one area of interest where extra efforts may be devoted.

MeSH terms: Neural tube defects; epidemiology; cluster analysis

La traduction du résumé se trouve à la fin de l'article.

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Neural tube defects (NTDs) are congenital abnormalities that result from incomplete closure of the developing neural tube during the fourth week of gestation.¹ Anencephaly, spina bifida cystica, and encephalocele account for most of the NTDs.² These conditions contribute significantly to both infant mortality and lifelong morbidity in affected individuals. Other spinal dysraphisms may include a less severe form, spina bifida occulta (a common condition that occurs in up to 20% of the general population^{3,4}), diastematomyelia, and lipomyelomeningocele. These less common spinal dysraphisms may also be concurrently associated with anencephaly, spina bifida cystica, and encephalocele.

The two most commonly attributed risk factors for NTDs are either the lack of dietary folic acid or a strong familial component.⁵ Failure to consume folic acid, either through fortified supplements or through multivitamins, increases the risk of having an affected child two- to eightfold.⁶ Risk is related to both maternal intake⁷ and maternal folic acid status.⁸ A family history of spina bifida cystica or anencephaly is one of the strongest risk factors and confers a risk of 3-8% to siblings of affected individuals.^{9,10} This familial aggregation is complex and multiple genes likely contribute. Implicated genes include those of the folate-homocysteine pathway¹¹ – others are currently being investigated.⁵ Aside from folic acid and familial contributions, additional factors may include Vitamin B12 insufficiency,¹² valproic acid¹³ and carbamazepine¹⁴ use, and maternal pregestational diabetes.¹⁵

The introduction of a folic acid supplementation program has been shown to reduce the rate of NTDs up to 85%.¹⁶ A folic acid supplementation program was implemented in Canada in 1996 to reduce the incidence of NTD births.

This study investigates the spatial distribution of spina bifida incidence in Newfoundland and Labrador (NL) by means of both a heterogeneity analysis and a Bayesian cluster analysis both before and after the implementation of the folic acid supplementation program. We determine if a residual spatial distribution remains. Only one other example of Bayesian spatial analysis applied to NTDs has been identified.¹⁷

METHODS

Case ascertainment

The Health Care Corporation of St. John's (NL) Medical Genetics Program ascertains cases of neural tube defects annually and maintains an NTD database. The database has recorded cases of NTDs since 1977. Cases are identified in the following ways: provincial live birth and stillbirth notification forms, maternal-fetal medicine referrals (only one tertiary care unit in the province), and letters sent to all medical record departments of all provincial hospitals requesting data on cases coded by ICD-9/10 codes associated with NTD or terminations for NTD. These multiple courses are utilized to ensure complete ascertainment.

The classification of malformations of the central nervous system proposed by EUROCAT is used.¹⁸ NTDs include anencephaly, craniorachischisis, iniencephaly, spina bifida cystica, cranial meningocele, encephalocele, and diastematomyelia and diplomyelia associated with open lesions. Spina bifida occulta, characterized by a defect of a single vertebral arch, was excluded as were cases of NTD associated with documented chromosome problems (e.g., Trisomy 18) and single gene disorders (e.g., Meckel Gruber syndrome).

Additionally, cases were ascertained by case searches via the Spina Bifida clinic at the Charles A. Janeway Child Health Centre in St. John's, the sole tertiary pediatric referral centre. Hence, yearly records of all spina bifida patients assessed at the Janeway Centre from 1977 to 2002 and seen in travelling clinics throughout the province provide comprehensive statistical data on most living patients.

NL is divided into 10 major census divisions and the island portion of the province is further divided into 79 consolidated census subdivisions. The Newfoundland and Labrador Centre for Health Information provided the live birth and population statistics for these census divisions and subdivisions.

Inclusion/exclusion criteria

All cases of anencephaly and spina bifida (including myelomeningocele and meningocele) are included in these analyses. Patients with encephalocele

TABLE I

Type and Number of Spinal Dysraphisms

Type of Dysraphism	Number of Cases
Anencephaly	231
with encephalocele	4
with spina bifida	59
Spina bifida	328
with encephalocele	4
Subtotal analyzed	626
Diastematomyelia	1
Dipomyelia	1
Encephalocele	35
Hydromyelia	1
Occulta	16
Total dysraphisms	680

Figure 1. Incidence of Spina Bifida in Newfoundland and Labrador from 1975 to 2002

(only) were not included since the incidence of encephalocele has not declined with the implementation of other folic acid programs,^{2,19} and one of the goals of this current study is to determine a set of residual cases from the targeting of one mechanism of disease (namely the contribution of folic acid supplementation). Patients with spina bifida occulta, diastematomyelia, lipomyelomeningocele and lipomeningocele were not included since these can be asymptomatic and part of spina bifida occulta. Including these cases would introduce a referral bias into our geographical analysis that would confound our interpretation of any variation noted. However, if these anomalies were associated with a spina bifida or anencephaly, that patient would be included.

Statistical analysis

Analysis of spatial variation of disease was conducted over 79 census-consolidated subdivisions. Because the area-specific number of cases can be small, traditional

statistical methods of analysis tend to yield very extreme rates due to random variation. Therefore, directly mapping incidence rates may cause the observer to draw incorrect conclusions due to visual attention to the extremes. A hierarchical Bayesian approach overcomes this by accounting for both the small number of counts and for the estimates of neighbouring regions (a conditional autoregressive model).²⁰ This method assumes the underlying relative risks follow an *a priori* probability distribution. An estimate that compromises between the area-specific risk and the average of the neighbouring areas' risks is simulated.²¹⁻²⁴ Estimates are "smoothed" more, that is, pulled more towards the mean, when the original number of counts is small without local evidence supporting the extreme value. This Bayesian estimate may better represent the true geographical risk variation.

A binomial model was assumed to obtain Bayesian estimates through Gibbs sampling^{24,25} on BUGS software²⁶ and

TABLE II

Number of NTD Occurrences (includes births and terminations) Prior to (1977-1996) and After (1997-2002) Implementation of the Folic Acid Program

Census Division	Pre Program Implementation 1977-1996			Post Program Implementation 1997-2002		
	NTD Births	All Births	NTD/All*1000 (95% CI)	NTD Births	All Births	NTD/All*1000 (95% CI)
1	290	51,995	5.58 (5.0-6.3)	16	14,148	1.13 (0.7-1.8)
2	36	5299	6.79 (4.9-9.4)	0	1314	0.00 (0.0-2.9)
3	23	3531	6.51 (4.3-9.7)	2	858	2.33 (0.6-8.4)
4	17	4671	3.64 (2.2-5.8)	0	1146	0.00 (0.0-3.3)
5	35	8320	4.21 (3.0-5.8)	1	2127	0.47 (0.1-2.7)
6	47	7024	6.69 (5.0-8.9)	4	2037	1.96 (0.8-5.1)
7*	30	7016	4.28 (3.0-6.1)	5	1782	2.81 (1.2-6.5)
8	53	6744	7.86 (6.0-10.)	2	2121	0.94 (0.2-3.4)
9	33	4098	8.05 (5.8-11.0)	1	996	1.00 (0.2-5.7)
10	27	7965	3.39 (2.3-4.9)	0	2164	0.00 (0.0-1.8)
Total	591	106,663	5.54 (5.1-6.0)	31	28,693	1.08 (0.8-1.6)

* Census division 7 contains a subdivision of persistent increased risk after the implementation of the folic acid program even though the census division itself has a relative risk that is within the 95% confidence interval of the provincial risk

TABLE III

Variation in Relative Risks (RR – census subdivisinal risk compared to the average provincial risk) for NTDs Across 79 Census-consolidated Subdivisions in Newfoundland from Two Periods: 1977-1996 and 1997-2002

	Observed	Expected	Unsmoothed RR	Smoothed RR
1977-1996				
Minimum	0.00	0.00	0.00	0.86
5 th percentile	0.00	0.81	0.00	0.93
Median	3.00	3.25	0.86	1.00
Mean	6.73	6.73	0.95	1.02
95 th percentile	13.10	13.28	2.15	1.18
Maximum	190.00	201.02	3.31	1.38
1997-2002				
Minimum	0.00	0.00	0.00	0.95
5 th percentile	0.00	0.04	0.00	0.97
Median	0.00	0.18	0.00	0.99
Mean	0.37	0.37	0.92	1.01
95 th percentile	1.00	0.72	5.90	1.02
Maximum	11.0	10.96	9.86	1.34

Bayesian hierarchical methods were used for the smoothed estimates

included both a spatially unstructured extrabinomial variation (heterogeneity) and a spatially structured variation (clustering).^{27,28} Specifically, the conditional autoregressive model was used. Convergence at 10,000 iterations was checked by visual examination of sample traces by Geweke's diagnostic²⁹ implemented in the CODA software.³⁰ A burn in of 10,000 iterations was performed and a subsequent 20,000 iterations were used in the final analysis.

Two different hyperprior distributions were compared for simulation. One was based on a model as $\Gamma(1,1)$ and the other a model as $\Gamma(0.5,0.0005)$ as per Bernardinelli et al.³¹ There was very little variation in the results between distribution choices, so the $\Gamma(0.5,0.0005)$ distribution was used.³²

This research was approved by the St. John's Health Care Corporation Human Investigation Committee.

RESULTS

A total of 680 cases were identified from 1977 to 2002. Table I shows the types and number of dysraphisms found. Six hundred twenty-six cases (347 female, 244 male, 35 unknown) with either anencephaly or spina bifida (or both) met the inclusion criteria and were included in the spatial analysis. The birth location for four cases could not be determined. Figure 1 shows the annual incidence of spina bifida from 1975 to 2002, demonstrating a sharp decline in cases after 1996, attributed to the implementation of the folic acid supplementation program in 1996.

The incidence of NTD births over the study period for each census division is shown in Table II. There was significant heterogeneity with the variation in rates across the census divisions (Pothoff and Whittinghill test, $p=0.002$). (The variability in the observed relative risks was greater

than that expected by chance if the rate ratios were the same for all areas in the study.) However, the smoothed relative risks showed considerably less variation between the 5th and 95th percentiles than the unsmoothed risk estimates for both periods under study after Bayesian estimation was employed. The smoothed relative risk estimates are quite uniform across the province for the period 1977-1996, and for 1997-2002. There are fewer cases after the implementation of the supplementation program (34 compared to 592 before the program implementation).

DISCUSSION

Recent implementations of folic acid supplementation programs worldwide have demonstrated remarkable success in reducing the rates of NTD births, with some programs reporting reductions of up to 50%.² The supplementation program in Newfoundland and Labrador has also achieved success, as Figure 1 demonstrates. Since the implementation of this program, the rate of spina bifida and anencephaly has dropped from 5.54 to 1.08 per 1000 live births.

Generally, the scientific reason for studying disease clusters is to implicate causality in the etiopathogenesis.³³ The Pothoff and Whittinghill test did suggest a significant heterogeneity in risk across major census divisions – the variability in the observed relative risks was greater than that expected by chance if the risk ratios were the same across census divisions. However, the results in Table III demonstrate that the smoothed relative risks showed considerably less variation between the 5th and 95th percentiles (0.93 to 1.18) than the unsmoothed relative risks (0.00 to 2.15) for the period from 1977 to 1996 when the small area analysis was done at the census consolidated subdivision level. There was one census-consolidated subdivision (Table II) with a pre-supplementation excess of 38% cases over the number expected (after smoothing) when both structured (local spatial) and unstructured heterogeneity is accounted for in the conditional autoregressive model used.^{24,27} This region continues to maintain a higher than average relative risk (an excess of 34% of cases) after the implementation of the folic acid supplementation program, even

though the risk in the entire census division generally reflects the overall risk. It is a smaller island that is accessible via ferry and although it may have a local hospital, it may not have had quite the same initial access to either education about folic acid or fortified food products (or both). As well, this census subdivision may be a genetic isolate (proven in other regions³⁴), and therefore the local population may have increased genetic risk for NTDs as demonstrated in other populations.⁵ The excess risk in this subdivision may also be an artifact of scale, given that the entire division presents with a normal relative risk, although this is unlikely given that unstructured heterogeneity was accounted for. One region on the west coast had a lower than expected relative risk (0.86), although this was only 14% lower than the average expected risk.

The time period after supplementation also demonstrated considerably less variation between the 5th and 95th percentiles (0.97 to 1.02) compared to the unsmoothed relative risks (0.00 to 5.90). This marked decrease in variation is again due to both structured and unstructured variation that is accounted for in Bayesian hierarchical modeling. For most regions (70 of 79), both prior to and after the implementation of the supplementation program, the variation in relative risk across the province is within 10% of the expected risk for each time period, suggesting that any local variation may be strictly due to both spatially unstructured and spatially (regionally) structured variation. The implications of this observation to the management of the public health initiative are that overall response to the decrease in cases tended to be uniform across the province, with potentially one area of interest where extra effort may be devoted.

A potential problem with this study is the fact that we did not standardize for socio-economic status across census-consolidated subdivisions. Although not confirmed as a significant risk factor,⁵ some studies have shown socio-economic status to be inversely related to the rate of NTD births.³⁵ This study attempted to localize regions of residually higher relative risk, regardless of socio-economic status, to further aid in public health efforts. In order to make further comment on etiology from residually high relative risks, socio-

economic status could be accounted for, although it is likely that there is significant uniformity of socio-economic status across rural Newfoundland.

We feel that our case ascertainment is near complete given our methods, and therefore we do not feel there is significant ascertainment bias. Given that there is very little geographical variability across census-consolidated subdivisions once the risks are smoothed, this study also suggests that there may not be any immediately obvious significant environmental or genetic factors influencing the risk across regions other than those already mentioned above.

CONCLUSIONS

This small area cluster analysis indicated that there was only one census-consolidated subdivision that demonstrated persistent increased risk after implementation of the folic acid supplementation program. Further investigation of this region from a public health perspective may aid in understanding the implications of both a prior and a residually high relative risk.

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RÉSUMÉ

Contexte : L'incidence des anomalies du tube neural (ATN) diminue partout dans le monde depuis l'avènement des programmes de supplémentation en acide folique. Un tel programme a été mis en œuvre à Terre-Neuve-et-Labrador (Canada) en 1996-1997. Nous avons étudié la répartition géographique des taux d'ATN à la naissance avant et après la mise en œuvre du programme pour déterminer les régions où ces taux demeurent élevés. Les cas excédentaires résiduels pourraient avoir des causes génétiques ou s'expliquer par une mise en œuvre incomplète du programme de supplémentation.

Méthode : Pour obtenir la quasi-totalité du nombre de cas, nous avons recueilli des données sur le lieu de résidence de la mère pour tous les avis de naissances vivantes et d'accouchements de morts-nés, les orientations en médecine materno-fœtale, les orientations en réadaptation, ainsi que tous les hôpitaux ayant déclaré des ATN ou des interruptions de grossesse en raison d'ATN dans la province pour la période de 1975 à 2002. Nous avons effectué des analyses bayésiennes par petits territoires pour les cas de 1975 à 1996 et pour ceux de 1997 à 2002, puis comparé les deux périodes.

Résultats : L'incidence des ATN à la naissance a diminué après 1996, passant de 5,54 p. 1 000 naissances vivantes à 1,08 p. 1 000 naissances vivantes. Nous avons recensé 592 cas entre 1975 et 1996, et 34 cas entre 1997 et 2002. Le risque relatif d'incidence de ces naissances était de 0,93 à 1,18 (IC de 95 %) entre 1975 et 1996 et de 0,97 à 1,02 entre 1997 et 2002, après lissage bayésien. Dans une seule région, les cas excédentaires résiduels étaient supérieurs à 34 %.

Conclusions : Pour la gestion de l'initiative de santé publique que représente la supplémentation en acide folique, nos observations montrent que la réponse globale à la diminution des cas a tendance à être uniforme à l'échelle de la province, mais qu'il existe une région où il faudrait peut-être consacrer des efforts supplémentaires.

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