The Global Burden of Neural Tube Defects and Disparities in Neurosurgical Care

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BACKGROUND: **Despite the success of folic acid fortification programs, neural tube defects (NTDs) such as spina bifida, encephalocele, and anencephaly remain among the most substantial causes of childhood morbidity and mortality worldwide. Although these are complicated conditions that require an interdisciplinary approach to care, definitive treatment of survivable NTDs is often neurosurgical.**

METHODS: **Using Global Burden of Disease data, we examined the global burden of NTDs as related to a nation's wealth, health care quality, and access to neurosurgical care. We abstracted data for death by cause, years lived with disability (YLD), gross domestic product (GDP), United Nations geoscheme, Food Fortification Initiative participation, and Healthcare Access and Quality Index. We compared means using 1-way analysis of variance and proportions using Fisher exact tests, with statistical significance as $\alpha = 0.05$.**

RESULTS: **Seventeen of 20 (85%) nations with the most deaths caused by NTDs ($P < 0.0001$) and 15/20 (75%) nations with the highest YLD ($P < 0.0001$) were in the lowest GDP quartile. Deaths and YLD were negatively correlated with increasing GDP and Healthcare Access and Quality Index ($P < 0.0001$). The nations with the highest disease burdens also had the fewest neurosurgeons per capita.**

CONCLUSIONS: **Despite the success of folic acid fortification programs, greater global public health efforts should be placed on improving access to neurosurgical care in low and middle-income nations through sustainable initiatives such as surgeon exchange programs and the establishment of neurosurgery residency training programs.**

INTRODUCTION

Neural tube defects (NTDs) including spina bifida, encephalocele, and anencephaly are among the most substantial causes of childhood morbidity and mortality worldwide.[1-4] They have been associated with a variety of environmental and genetic risk factors. Environmental risk factors include teratogens such as valproic acid and fungal-derived fumonisin, as well as maternal obesity, diabetes, fever, use of hot tubs, and folate deficiency.[5-11] Genetic causes are generally believed to be polygenic and complex,[12,13] although some genes related to folic acid metabolism have been associated with NTDs.[14,15] Many nations now have mandated folic acid fortification requirements for food products such as wheat and maize flour to prevent NTDs.[1,16] Many NTDs are now prevented worldwide each year, likely driven by the success of those programs and increasing awareness of the importance of preconception folic acid supplementation.[1,4]

Despite the success of campaigns to improve folic acid supplementation in many parts of the world, NTDs continue to occur and lead to significant morbidity, mortality, and economic cost.[1,17] Spina bifida can result in damage to the spinal cord and nerves, leading to impairment or loss of motor, sensory, and autonomic function (e.g., neurogenic bladder).[18] Encephalocele can entail

Key words
- Folic acid
- Global Burden of Disease
- Neural tube defects
- Spina bifida

Abbreviations and Acronyms
FFI: Food Fortification Initiative
GBD: Global Burden of Disease
GDP: Gross domestic product
HAQ: Healthcare Access and Quality
NTD: Neural tube defect
SD: Standard deviation
YLD: Years lived with disability

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cerebral herniation and thus result in cognitive impairment in addition to other neurologic impairment.[19] Patients living with any NTD may also have significant cosmetic concerns that contribute to morbidity, such as craniofacial abnormalities caused by encephaloceles, and can also be affected psychologically and financially because of their condition.[17] Although these are complicated conditions that require an interdisciplinary approach to care, definitive treatment of survivable NTDs is often neurosurgical.[19]

Several groups have estimated the global burden of disease caused by NTDs through the use of birth defect registries, literature reviews, modeling strategies, or a combination of these 3 approaches. The most recent and comprehensive of such studies was reported by Blencowe et al. in 2018.[20] This group estimated that 260,000 pregnancies were affected by NTDs worldwide in 2015. The regions with the most NTD-affected birth outcomes per capita were Southern Asia, East Asia, and Northern Africa and Western Asia. The regions with the fewest NTD-affected birth outcomes were North America, Latin America and the Caribbean, and Europe.

The Global Burden of Disease (GBD) study is an international collaboration and the largest investigation into worldwide disease burden ever conducted. It is funded in large part by the Bill and Melinda Gates Foundation, and it is based at the University of Washington. This project includes 1800 researchers from 127 nations, with data collected on 195 nations. Data from this study are open source and available for free download. They are collected from a variety of sources, including surveys, registries, literature reviews, and reporting partnerships with regional and local public health entities. NTDs are among the conditions that have been included in the GBD database, although the ability to resolve specific subtypes is not yet available (as of February 17, 2021), nor is information available about the prevalence of particular NTD risk factors (e.g., folate deficiency or obesity).

In the present study, we used GBD data to examine the global burden of NTDs. We determined how this burden is distributed geographically and related to a nation's wealth and the quality of its health care system. We also looked at existing data on global neurosurgical infrastructure. We hypothesized that low-income nations would have both a disproportionately large share of the global burden of NTDs and low levels of the neurosurgical infrastructure required to definitively address them.

METHODS

Using GBD data, we abstracted data for death by cause and years lived with disability (YLD) for NTDs for every nation in the world for 1990–2019. Using data from the United Nations Statistics Division, we determined gross domestic product (GDP) per capita for each nation for 2019. We constructed bar graphs to visually correlate the global burden of NTDs with GDP per capita. We performed regional analyses by grouping nations in accordance with the United Nations geoscheme. We used data from the Food Fortification Initiative (FFI) to see which nations had folic acid fortification programs in 2018. We used the 2016 Healthcare Access and Quality (HAQ) Index to represent the quality of the health care system of each nation. All data were selected from the most recent year for which complete data were available. We compared all this information among nations, with particular attention paid to how socioeconomic status was related to prevalence of NTD-attributable morbidity and mortality. We examined trends in global NTD disease burden over time using the GBD graphical user interface. We conducted a comprehensive review of the literature on global neurosurgical infrastructure and compared this with the global burden of NTDs. We compared means between groups using 1-way analysis of variance with Tukey post hoc tests and proportions using Fisher exact tests. Statistical significance was taken as $\alpha = 0.05$.

RESULTS

The United Nations geoscheme; GDP per capita and GDP per capita quartile for 2019; HAQ index and HAQ index quartile for 2016; folic acid fortification in food staples in parts per million most recently accessed on January 18, 2021; deaths and YLD for 1990 and 2019 and their absolute changes per 100,000 persons for 191 nations are summarized in **Table 1**. All 20 of the 20 nations (100%) with the most deaths caused by NTDs in 2019 were in the lowest 2 GDP quartiles and 17 of 20 nations (85%) with the most deaths caused by NTDs were in the lowest quartile ($P < 0.0001$). Of the 20 nations with the highest YLD, 15 (75%) were in the lowest GDP quartile, 4 (20%) were in the second lowest, and 1 (5%) was in the third lowest ($P < 0.0001$). In 186 of 191 nations (97%), there was a reduction in deaths from NTDs in 2019 compared with 1990. Nevertheless, only 107/186 of these reductions (58%) were statistically significant. Japan was the only nation with a statistically significant increase in deaths attributed to NTDs during the study period. There was a reduction of YLD in 149 of 191 nations (78%). Nevertheless, Iran was the only nation with a statistically significant reduction in YLD attributed to NTDs during the study period. Norway was the only nation with a statistically significant increase. Of the 20 countries with the greatest decrease in deaths, 17 (85%) were in the lowest GDP quartile, 2 (10%) were in the second, and 1 (5%) was in the third ($P < 0.0001$). Seventeen (85%) were in the lowest HAQ index quartile, and 3 (15%) were in the second-lowest quartile ($P < 0.0001$).

Of the 20 nations with the highest deaths caused by NTDs in 2019, 12 (60%) had documented folic acid fortification programs, including Burkina Faso, Mali, Niger, Sierra Leone, Nigeria, Afghanistan, Guinea, Benin, Côte d'Ivoire, Yemen, Cameroon, and Mozambique. All 12 of those nations experienced a decrease in deaths attributable to NTDs between 1990 and 2019, but no decrease was statistically significant. Nevertheless, all 8 of the remaining nations without folic acid fortification programs experienced a decrease in deaths attributable to NTDs between 1990 and 2019, although none of these decreases were statistically significant. Of the 20 nations with the highest YLD, 15 (75%) had documented folic acid fortification programs, including Uganda, Guinea, Nigeria, Benin, Côte d'Ivoire, Burkina Faso, Sierra Leone, Cameroon, Mali, Togo, Burundi, Liberia, Ghana, Niger, and Paraguay. Twelve of those 15 nations (80%) experienced a decrease in YLD between 1990 and 2019. Nevertheless, 3 of the 5 remaining nations (60%) without folic acid fortification programs experienced a decrease in YLD attributable to NTDs between 1990 and 2019 ($P = 0.76$) (**Table 1**).

Table 1. United Nations Geoscheme, Gross Domestic Product per Capita and Gross Domestic Product per Capita Quartile for 2019, Healthcare Access and Quality Index and Healthcare Access and Quality Index Quartile for 2016, Folic Acid Fortification in Food Staples in Parts per Million, Deaths and Years Lived with Disability for 1990 and 2019 and Their Absolute Changes for 191 Nations

Country	United Nations Geoscheme	GDP per Capita ($)	GDP per Capita Quartile	HAQ Index	HAQ Index Quartile	Folic Acid Fortification (ppm)	Deaths 1990 (n)	Deaths 2019 (n)	Change in Deaths 1990–2019	YLD 1990 (n)	YLD 2019 (n)	Change in YLD 1990–2019
Afghanistan	Southern Asia	470	1	32.5	1	1 in wheat	26.84	7.83	−19.02	7.55	6.77	−0.78
Albania	Southern Europe	5303	2	78.2	4		1.62	0.30	−1.32	2.38	2.07	−0.31
Algeria	Northern Africa	3976	2	63.7	3		4.98	0.92	−4.06	4.67	3.31	−1.36
Andorra	Southern Europe	40,887	4	94.6	4		0.09	0.03	−0.07	2.25	1.96	−0.30
Angola	Middle Africa	2671	2	40.7	1		13.06	3.91	−9.15	10.98	9.13	−1.85
Antigua and Barbuda	Caribbean	17,113	3	66.7	3		0.31	0.15	−0.16	2.25	2.49	0.24
Argentina	South America	10,041	3	68.4	3	2.2 in wheat	1.09	0.50	−0.59	8.13	6.27	−1.86
Armenia	Western Asia	4623	2	67.5	3		1.59	0.54	−1.05	5.76	4.18	−1.59
Australia	Australia and New Zealand	54,763	4	89.8	4	2.5 in wheat	0.40	0.17	−0.23	3.62	3.17	−0.46
Austria	Western Europe	49,701	4	88.2	4		0.15	0.12	−0.03	2.17	2.84	0.66
Azerbaijan	Western Asia	4782	2	64.5	3		1.64	0.20	−1.44	4.70	3.03	−1.67
Bahamas	Caribbean	34,864	4	63.9	3		0.33	0.13	−0.20	2.47	2.56	0.09
Bahrain	Western Asia	23,504	4	79.0	4	1.5 in wheat	2.27	0.21	−2.06	3.57	2.50	−1.07
Bangladesh	Southern Asia	1846	2	51.7	2	1.7 in rice	6.14	0.78	−5.36	6.23	4.55	−1.68
Barbados	Caribbean	18,149	4	66.8	3		0.17	0.08	−0.09	1.74	1.97	0.23
Belarus	Eastern Europe	6674	3	74.4	3		1.06	0.23	−0.83	4.52	2.73	−1.79
Belgium	Western Europe	46,198	4	87.9	4		0.23	0.10	−0.13	3.43	3.66	0.23
Belize	Central America	4884	2	58.3	2	1.8 in wheat, 1.05 in rice	1.00	0.34	−0.66	3.14	3.15	0.00
Benin	Western Africa	1220	1	43.0	1	2.5 in wheat	14.07	6.93	−7.15	12.44	11.66	−0.79
Bermuda	Northern America	117,768	4	79.0	4		0.24	0.09	−0.14	2.02	2.07	0.05
Bhutan	Southern Asia	3361	2	52.7	2		4.74	0.63	−4.11	6.73	3.86	−2.87
Bolivia	South America	3552	2	59.2	2	1.5 in wheat	3.16	1.00	−2.16	4.13	4.38	0.24
Bosnia and Herzegovina	Southern Europe	6109	3	78.2	4		0.42	0.13	−0.29	2.44	2.52	0.08
Botswana	Southern Africa	7961	3	51.1	2		0.61	0.42	−0.18	4.78	3.69	−1.10
Brazil	South America	8755	3	64.9	3	1.8 in wheat and maize	2.47	0.82	−1.65	2.67	1.84	−0.83
Brunei	South-Eastern Asia	31,086	4	70.0	3		1.13	0.43	−0.70	6.27	5.62	−0.65

Deaths, years lived with disability, and all absolute changes are reported per 100,000 persons.
GDP, gross domestic product; HAQ, Healthcare Access and Quality; YLD, years lived with disability.

Continues

Table 1. Continued

Country	United Nations Geoscheme	GDP per Capita ($)	GDP per Capita Quartile	HAQ Index	HAQ Index Quartile	Folic Acid Fortification (ppm)	Deaths 1990 (n)	Deaths 2019 (n)	Change in Deaths 1990–2019	YLD 1990 (n)	YLD 2019 (n)	Change in YLD 1990–2019
Bulgaria	Eastern Europe	9703	3	71.4	3		0.49	0.12	−0.37	3.20	3.12	−0.07
Burkina Faso	Western Africa	787	1	42.9	1	2.5 in wheat	15.70	10.92	−4.78	10.62	11.12	0.50
Burundi	Eastern Africa	260	1	40.4	1	2.3 in wheat, 1.2 in maize	8.66	3.38	−5.27	10.41	9.71	−0.70
Cabo Verde	Western Africa	3604	2	61.7	2		4.00	0.65	−3.35	8.20	5.90	−2.30
Cambodia	South-Eastern Asia	1644	1	50.7	2	5 in wheat	7.04	0.99	−6.05	4.59	3.46	−1.13
Cameroon	Middle Africa	1534	1	44.4	1	1.5 in wheat	6.95	4.06	−2.90	11.49	10.86	−0.63
Canada	Northern America	46,550	4	87.6	4	2.6 in wheat	0.37	0.13	−0.23	3.21	1.88	−1.33
Central African Republic	Middle Africa	468	1	28.6	1		11.60	8.02	−3.59	11.75	12.13	0.39
Chad	Middle Africa	707	1	37.7	1		15.94	10.30	−5.64	10.99	11.75	0.76
Chile	South America	14,896	3	76.0	3	1.8 in wheat	1.31	0.39	−0.92	8.67	5.81	−2.86
China	Eastern Asia	10,004	3	74.2	3	2 in wheat	2.45	0.19	−2.26	1.78	1.25	−0.53
Colombia	South America	6432	3	67.8	3	1.54 in wheat	0.71	0.27	−0.44	6.77	5.83	−0.95
Comoros	Eastern Africa	1370	1	47.7	1		5.83	1.75	−4.08	8.20	6.05	−2.16
Congo	Middle Africa	2304	2	43.5	1		5.27	1.77	−3.50	9.67	7.79	−1.88
Costa Rica	Central America	12,238	3	72.9	3	1.8 in wheat and rice, 1.3 in maize	1.24	0.42	−0.83	6.41	5.03	−1.38
Côte d'Ivoire	Western Africa	2276	2	42.4	1	1.5 in wheat	10.21	4.73	−5.47	12.57	11.57	−1.00
Croatia	Southern Europe	14,627	3	81.6	4		0.06	0.08	0.02	2.48	2.81	0.33
Cuba	Caribbean	9296	3	73.5	3	1.85 in wheat	0.09	0.12	0.03	2.46	3.27	0.82
Cyprus	Western Asia	28,285	4	85.3	4		0.15	0.08	−0.07	4.39	3.98	−0.41
Czechia	Eastern Europe	23,452	4	84.8	4		0.42	0.10	−0.32	2.19	2.44	0.25
Democratic Republic of the Congo	Middle Africa	545	1	40.4	1		11.54	3.75	−7.79	14.10	13.42	−0.68
Denmark	Northern Europe	60,657	4	85.7	4		0.30	0.09	−0.21	4.27	4.40	0.13
Djibouti	Eastern Africa	3252	2	44.7	1	1.3 in wheat	5.44	2.21	−3.23	7.78	5.05	−2.74
Dominica	Caribbean	8111	3	58.1	2		0.46	0.37	−0.09	2.26	2.78	0.51
Dominican Republic	Caribbean	8282	3	62.5	2	1.8 in wheat and maize	1.51	0.28	−1.24	3.27	3.16	−0.10
Ecuador	South America	6184	3	61.2	2	1.7 in wheat	0.64	0.42	−0.22	4.34	4.97	0.63
Egypt	Northern Africa	3161	2	61.0	2		4.32	0.39	−3.93	4.79	3.69	−1.10
El Salvador	Central America	4187	2	64.4	3	1.8 in wheat, 1 in maize	3.97	0.50	−3.47	6.82	5.29	−1.52

Equatorial Guinea	Middle Africa	8130	3	48.4	1		10.54	1.31	−9.23	11.33	7.52	−3.81
Eritrea	Eastern Africa	567	1	38.1	1		6.48	2.20	−4.28	9.01	7.92	−1.09
Estonia	Northern Europe	23,740	4	81.4	4		0.46	0.06	−0.41	2.62	1.72	−0.90
Eswatini	Southern Africa	4002	2	41.9	1	1.5 in wheat	1.22	0.58	−0.65	5.54	4.63	−0.92
Ethiopia	Eastern Africa	828	1	44.2	1	2 in wheat	11.57	2.76	−8.81	7.22	5.61	−1.61
Fiji	Melanesia	6185	3	46.6	1	2 in wheat	1.45	0.66	−0.80	1.78	1.54	−0.24
Finland	Northern Europe	48,678	4	89.6	4		0.10	0.08	−0.02	2.30	2.60	0.30
France	Western Europe	40,319	4	87.9	4		0.15	0.09	−0.07	3.25	3.66	0.41
Gabon	Middle Africa	7773	3	51.4	2		4.92	1.23	−3.69	8.55	6.76	−1.78
Gambia	Western Africa	776	1	49.7	2		7.35	2.47	−4.87	10.76	8.46	−2.30
Georgia	Western Asia	4439	2	62.1	2		0.34	0.24	−0.10	4.70	3.79	−0.91
Germany	Western Europe	46,232	4	86.4	4		0.10	0.12	0.02	3.55	4.50	0.95
Ghana	Western Africa	2203	2	49.7	2	2.08 in wheat	5.27	2.56	−2.71	10.96	9.32	−1.64
Greece	Southern Europe	19,604	4	87.0	4		0.38	0.15	−0.23	2.87	2.72	−0.15
Greenland	Northern America	53,353	4	71.0	3		1.54	0.27	−1.27	1.85	1.23	−0.62
Grenada	Caribbean	10,818	3	58.3	2		0.54	0.30	−0.24	2.82	2.89	0.07
Guatemala	Central America	4363	2	55.7	2	0.4 in wheat, 1.35 in maize	2.22	0.82	−1.40	6.22	5.00	−1.22
Guinea	Middle Africa	967	1	38.6	1	1.35 in wheat	17.12	7.56	−9.56	12.14	11.91	−0.23
Guinea-Bissau	Western Africa	688	1	36.3	1		15.17	5.16	−10.02	14.24	12.00	−2.24
Guyana	South America	6610	3	49.8	2		0.74	0.32	−0.42	3.39	3.01	−0.38
Haiti	Caribbean	715	1	38.5	1		11.27	4.63	−6.64	5.58	5.78	0.20
Honduras	Central America	2575	2	53.9	2	1.8 in wheat	1.47	0.56	−0.91	5.72	5.03	−0.69
Hungary	Eastern Europe	16,879	3	79.6	4		0.32	0.12	−0.20	1.94	2.19	0.25
Iceland	Northern Europe	71,345	4	93.6	4		0.12	0.12	0.00	2.53	3.02	0.49
India	Southern Asia	2116	2	44.8	1	1.3 in wheat and rice	3.04	0.58	−2.46	7.08	5.48	−1.60
Indonesia	South-Eastern Asia	4136	2	49.2	1	2 in wheat	2.91	0.56	−2.35	2.82	1.84	−0.98
Iran	Southern Asia	7282	3	71.1	3		5.00	0.32	−4.68	5.67	2.48	−3.18
Iraq	Western Asia	5730	3	60.1	2	2.1 in wheat	3.17	0.54	−2.63	6.31	3.77	−2.54
Ireland	Northern Europe	81,637	4	88.4	4		1.04	0.21	−0.83	7.77	5.22	−2.55
Israel	Western Asia	46,376	4	85.5	4		0.57	0.25	−0.32	4.13	4.18	0.04
Italy	Southern Europe	33,090	4	88.7	4		0.15	0.07	−0.08	1.20	1.30	0.10
Jamaica	Caribbean	5369	2	63.7	3		0.41	0.13	−0.27	2.34	2.49	0.15

Deaths, years lived with disability, and all absolute changes are reported per 100,000 persons.
GDP, gross domestic product; HAQ, Healthcare Access and Quality; YLD, years lived with disability.

Continues

Table 1. Continued

Country	United Nations Geoscheme	GDP per Capita ($)	GDP per Capita Quartile	HAQ Index	HAQ Index Quartile	Folic Acid Fortification (ppm)	Deaths 1990 (n)	Deaths 2019 (n)	Change in Deaths 1990–2019	YLD 1990 (n)	YLD 2019 (n)	Change in YLD 1990–2019
Japan	Eastern Asia	40,063	4	89.0	4		0.05	0.08	0.03	2.85	3.07	0.22
Jordan	Western Asia	4405	2	76.5	3	1.52 in wheat	0.66	0.32	−0.34	3.23	2.79	−0.45
Kazakhstan	Central Asia	9793	3	61.1	2	1.4 in wheat	0.89	0.38	−0.51	4.72	3.79	−0.93
Kenya	Eastern Africa	1817	2	48.7	1	1.5 in wheat and maize	3.28	1.09	−2.19	8.24	6.32	−1.92
Kiribati	Micronesia	1657	1	44.9	1	2 in wheat	4.08	1.26	−2.82	3.61	2.64	−0.97
Kuwait	Western Asia	31,999	4	82.0	4	1.75 in wheat	0.95	0.25	−0.70	4.51	3.31	−1.20
Kyrgyzstan	Central Asia	1318	1	60.4	2		1.29	0.63	−0.66	5.87	4.62	−1.25
Laos	South-Eastern Asia	2625	2	44.9	1		9.20	1.59	−7.61	4.84	3.84	−1.00
Latvia	Northern Europe	17,885	4	77.7	4		0.81	0.06	−0.76	4.08	2.46	−1.62
Lebanon	Western Asia	7784	3	80.0	4		2.12	0.35	−1.77	4.10	2.92	−1.18
Lesotho	Southern Africa	1158	1	35.7	1		1.36	0.70	−0.67	5.68	4.79	−0.89
Liberia	Western Africa	523	1	45.4	1	2.6 in wheat	16.25	2.66	−13.59	11.79	9.51	−2.28
Libya	Northern Africa	4810	2	69.9	3		3.59	0.42	−3.17	4.74	3.12	−1.62
Lithuania	Northern Europe	19,795	4	76.6	3		1.02	0.13	−0.90	5.06	3.06	−2.01
Luxembourg	Western Europe	115,481	4	89.3	4		0.25	0.07	−0.18	2.64	2.29	−0.36
Madagascar	Eastern Africa	523	1	43.7	1		6.90	2.42	−4.48	8.85	7.46	−1.39
Malawi	Eastern Africa	435	1	47.0	1	2 in wheat, 1 in maize	10.66	2.44	−8.21	10.43	8.70	−1.72
Malaysia	South-Eastern Asia	11,414	3	66.6	3		0.90	0.26	−0.64	3.10	2.64	−0.46
Maldives	Southern Asia	10,626	3	75.5	3		2.04	0.25	−1.79	3.06	1.79	−1.27
Mali	Western Africa	887	1	45.6	1	2.5 in wheat	18.89	10.71	−8.19	9.97	10.80	0.83
Malta	Southern Europe	33,752	4	85.1	4		0.73	0.18	−0.56	5.55	4.38	−1.18
Marshall Islands	Micronesia	4038	2	49.8	2		1.82	0.61	−1.21	3.05	2.32	−0.73
Mauritania	Western Africa	1678	1	52.0	2		7.65	2.10	−5.54	7.83	7.29	−0.55
Mauritius	Eastern Africa	11,169	3	65.7	3		0.36	0.20	−0.16	2.52	1.78	−0.74
Mexico	Central America	9849	3	62.6	3	2 in wheat and maize	2.73	0.57	−2.16	7.89	3.67	−4.22
Micronesia	Micronesia	3640	2	53.8	2		2.22	0.34	−1.88	2.97	2.11	−0.86
Moldova	Eastern Europe	2957	2	73.1	3	1.4 in wheat	1.38	0.18	−1.20	3.83	2.40	−1.43
Monaco	Western Europe	190,532	4	73.1	3		0.15	0.05	−0.11	1.77	1.85	0.09
Mongolia	Eastern Asia	4295	2	58.5	2		0.77	0.20	−0.57	5.50	3.84	−1.66
Montenegro	Southern Europe	8825	3	80.7	4		0.08	0.01	−0.07	1.61	1.61	0.00

Morocco	Northern Africa	3282	2	61.3	2	1.53 in wheat	4.06	0.43	−3.63	4.51	3.11	−1.40
Mozambique	Eastern Africa	504	1	43.0	1	2 in wheat and maize	10.15	4.02	−6.12	9.76	8.52	−1.24
Myanmar	South-Eastern Asia	1421	1	48.4	1		5.46	1.48	−3.98	4.80	3.47	−1.33
Namibia	Southern Africa	4957	2	53.7	2		0.83	0.38	−0.44	4.40	3.81	−0.59
Nepal	Southern Asia	1074	1	50.8	2	1.5 in wheat	5.55	0.58	−4.97	6.24	4.60	−1.64
Netherlands	Western Europe	53,053	4	89.5	4		0.47	0.16	−0.31	4.14	3.59	−0.56
New Zealand	Australia and New Zealand	43,264	4	86.2	4		0.57	0.21	−0.36	1.47	1.83	0.36
Nicaragua	Central America	1913	2	64.3	3	1.8 in wheat, 1 in rice	2.30	0.55	−1.75	5.70	4.43	−1.27
Niger	Western Africa	555	1	41.0	1	2.5 in wheat	20.40	9.62	−10.78	8.14	9.16	1.02
Nigeria	Western Africa	2361	2	51.3	2	2.6 in wheat and maize	12.13	7.93	−4.20	12.03	11.76	−0.26
North Korea	Eastern Asia	640	1	62.3	2		2.14	0.13	−2.01	1.36	1.10	−0.26
North Macedonia	Southern Europe	6093	3	76.0	3		0.92	0.12	−0.80	2.22	2.10	−0.12
Norway	Northern Europe	74,986	4	90.5	4		0.11	0.10	−0.02	2.04	5.52	3.48
Oman	Western Asia	15,343	3	77.1	4		2.33	0.29	−2.04	5.75	3.82	−1.92
Pakistan	Southern Asia	1187	1	43.1	1		4.48	1.41	−3.07	4.13	4.05	−0.09
Palestine	Western Asia	3424	2	70.5	3	1.5 in wheat	2.30	0.61	−1.69	5.00	3.47	−1.54
Panama	Central America	15,728	3	64.4	3	1.8 in wheat, 1 in rice	0.65	0.43	−0.22	3.90	3.78	−0.12
Papua New Guinea	Melanesia	2845	2	38.6	1		5.61	3.42	−2.19	3.36	3.11	−0.26
Paraguay	South America	5406	3	60.4	2	3 in wheat	1.33	0.46	−0.87	9.74	9.06	−0.68
Peru	South America	6978	3	69.6	3	1.2 in wheat	1.19	0.33	−0.86	3.44	3.53	0.09
Philippines	South-Eastern Asia	3324	2	52.0	2		1.36	0.59	−0.77	5.59	5.76	0.18
Poland	Eastern Europe	15,727	3	79.6	4		0.77	0.13	−0.64	3.27	4.72	1.46
Portugal	Southern Europe	23,350	4	84.5	4		0.40	0.06	−0.34	4.74	3.78	−0.96
Puerto Rico	Caribbean	35,791	4	76.6	4		0.46	0.13	−0.33	3.42	2.64	−0.77
Qatar	Western Asia	64,782	4	85.2	4	1.75 in wheat	1.98	0.20	−1.78	2.93	2.11	−0.82
Romania	Eastern Europe	12,914	3	74.4	3		0.71	0.20	−0.51	2.98	2.64	−0.34
Russian Federation	Eastern Europe	11,606	3	71.7	3		0.27	0.16	−0.12	2.46	2.02	−0.44
Rwanda	Eastern Africa	820	1	47.8	1	1.2 in maize	7.26	1.86	−5.40	10.37	7.65	−2.72
Saint Lucia	Caribbean	11,611	3	62.5	2		0.70	0.20	−0.51	2.50	2.27	−0.23
Saint Vincent and the Grenadines	Caribbean	7464	3	57.5	2		1.14	0.38	−0.76	3.05	2.73	−0.32
Samoa	Polynesia	4285	2	62.1	2		1.08	0.23	−0.84	2.15	1.88	−0.27

Deaths, years lived with disability, and all absolute changes are reported per 100,000 persons.
GDP, gross domestic product; HAQ, Healthcare Access and Quality; YLD, years lived with disability.

Continues

Table 1. Continued

Country	United Nations Geoscheme	GDP per Capita ($)	GDP per Capita Quartile	HAQ Index	HAQ Index Quartile	Folic Acid Fortification (ppm)	Deaths 1990 (n)	Deaths 2019 (n)	Change in Deaths 1990–2019	YLD 1990 (n)	YLD 2019 (n)	Change in YLD 1990–2019
Sao Tome and Principe	Middle Africa	1961	2	49.6	2		6.66	1.45	−5.21	9.68	7.40	−2.27
Saudi Arabia	Western Asia	23,140	4	79.4	4	1.75 in wheat	5.82	0.15	−5.67	10.48	5.27	−5.21
Senegal	Western Africa	1452	1	44.4	1	2.5 in wheat	10.70	3.60	−7.10	10.13	8.95	−1.17
Serbia	Southern Europe	7359	3	75.4	3		0.45	0.06	−0.39	2.02	1.78	−0.24
Seychelles	Eastern Africa	17,382	4	66.1	3		0.66	0.30	−0.36	2.71	2.33	−0.38
Sierra Leone	Western Africa	528	1	41.3	1	2.08 in wheat	18.91	8.84	−10.07	11.92	10.96	−0.95
Singapore	South-Eastern Asia	64,103	4	86.3	4		0.52	0.10	−0.43	7.35	6.27	−1.08
Slovakia	Eastern Europe	19,256	4	78.6	4		0.22	0.06	−0.15	2.43	2.20	−0.23
Slovenia	Eastern Europe	26,062	4	87.4	4		0.19	0.04	−0.15	3.38	3.21	−0.17
Solomon Islands	Melanesia	1945	2	43.1	1	2 in wheat, 1.1 in rice	3.32	1.07	−2.24	3.79	2.87	−0.92
Somalia	Eastern Africa	105	1	34.2	1		9.24	6.08	−3.16	9.41	8.83	−0.57
South Africa	Southern Africa	6001	3	52.0	2	1.4286 in wheat, 1 in maize	0.73	0.47	−0.26	5.12	4.04	−1.08
South Korea	Eastern Asia	32,143	4	85.8	4		0.08	0.06	−0.02	3.46	3.35	−0.11
South Sudan	Eastern Africa	448	1	38.8	1		10.56	5.65	−4.91	7.23	7.46	0.23
Spain	Southern Europe	29,816	4	89.6	4		0.25	0.08	−0.16	4.43	3.95	−0.48
Sri Lanka	Southern Asia	3940	2	72.8	3		0.35	0.07	−0.28	2.40	1.89	−0.51
Sudan	Northern Africa	815	1	50.1	2		23.56	4.18	−19.39	8.37	6.56	−1.81
Suriname	South America	6360	3	56.7	2		2.54	0.83	−1.71	3.46	3.29	−0.17
Sweden	Northern Europe	52,896	4	90.5	4		0.15	0.17	0.02	2.36	3.00	0.64
Switzerland	Western Europe	85,135	4	91.8	4		0.13	0.12	−0.01	2.16	3.05	0.89
Syria	Western Asia	1194	1	74.6	3		4.55	0.46	−4.10	4.64	3.12	−1.51
Tajikistan	Central Asia	894	1	58.6	2		0.88	0.75	−0.13	4.74	4.76	0.02
Tanzania	Eastern Africa	1084	1	49.9	2	3 in wheat, 1.5 in maize	7.35	3.88	−3.47	9.24	8.57	−0.66
Thailand	South-Eastern Asia	1084	1	70.8	3		1.41	0.21	−1.19	3.39	2.13	−1.26
Timor-Leste	South-Eastern Asia	899	1	51.6	2		6.59	1.60	−5.00	4.76	3.95	−0.80
Togo	Western Africa	1561	1	44.3	1	2.6 in wheat	8.89	3.07	−5.83	11.88	10.28	−1.60
Tonga	Polynesia	4865	2	62.1	2		0.79	0.26	−0.53	1.84	1.69	−0.15
Trinidad and Tobago	Caribbean	16,637	3	62.1	2		0.43	0.14	−0.29	2.59	2.25	−0.34
Tunisia	Northern Africa	3318	2	70.1	3		3.80	0.32	−3.49	3.26	2.12	−1.14

Turkey	Western Asia	9127	3	76.2	3		4.90	0.55	−4.35	3.21	2.65	−0.55
Turkmenistan	Central Asia	8124	3	58.1	2	1.5 in wheat	1.06	0.56	−0.49	4.31	3.96	−0.35
Uganda	Eastern Africa	737	1	42.9	1	2.3 in wheat, 0.5 in maize	6.33	2.75	−3.58	15.29	13.98	−1.30
Ukraine	Eastern Europe	3496	2	72.7	3		0.85	0.42	−0.44	4.42	2.64	−1.78
United Arab Emirates	Western Asia	43,103	4	72.2	3	1.75 in wheat	1.64	0.10	−1.54	7.93	5.21	−2.71
United Kingdom	Northern Europe	41,855	4	84.6	4		0.26	0.19	−0.07	2.18	2.20	0.02
United States	Northern America	65,134	4	81.3	4	1.54 in wheat, 1.87 in maize, 2.31 in rice	0.31	0.23	−0.08	1.31	1.08	−0.23
Uruguay	South America	16,190	3	72.0	3	2.4 in wheat	0.72	0.32	−0.40	7.82	6.74	−1.08
Uzbekistan	Central Asia	1756	1	62.3	2		1.52	0.68	−0.84	6.82	4.39	−2.43
Vanuatu	Melanesia	3023	2	43.1	1		1.99	0.81	−1.19	2.85	2.54	−0.31
Venezuela	South America	4733	2	64.7	3		1.00	0.35	−0.65	4.67	3.68	−0.99
Vietnam	South-Eastern Asia	2715	2	66.3	3	5.11 in wheat	1.93	0.23	−1.69	5.10	2.75	−2.35
Yemen	Western Asia	855	1	49.6	2	1.5 in wheat	16.48	4.32	−12.16	7.18	6.23	−0.95
Zambia	Eastern Africa	1292	1	41.6	1		8.11	2.37	−5.74	10.08	8.31	−1.78
Zimbabwe	Eastern Africa	1464	1	48.7	1	2 in wheat, 1.3 in maize	0.76	0.76	0.00	5.22	5.20	−0.02

Deaths, years lived with disability, and all absolute changes are reported per 100,000 persons.
GDP, gross domestic product; HAQ, Healthcare Access and Quality; YLD, years lived with disability.

Table 2. Neural Tube Defect–Specific Average Deaths and Years Lived with Disability and Their Sum for 1990 and 2019, Average Change in Those Values, and Nations with Folic Acid Fortification for Each Gross Domestic Product Quartile

Gross Domestic Product per Capita Quartile	Average Deaths in 2019, n (SD)	Average YLD in 2019, n (SD)	Average Deaths in 1990, n (SD)	Average YLD in 1990, n (SD)	Deaths + YLD 2019 (n)	Deaths + YLD 1990 (n)	Average Change in Deaths 2019–1990, n (SD)	Average Change in YLD 2019–1990, n (SD)	Average Change in Deaths + YLD 2019–1990	Countries with Folic Acid Fortification, n (%)
1 (lowest)	3.70 (3.00)	7.59 (3.19)	9.61 (6.12)	8.52 (3.16)	11.29	18.13	−5.91 (4.14)	−0.93 (0.89)	−6.84	23 (49)
2	1.02 (1.40)	4.29 (2.35)	3.36 (2.91)	5.44 (2.62)	5.31	8.80	−2.34 (1.93)	−1.14 (0.75)	−3.49	21 (44)
3	0.36 (0.26)	3.49 (1.68)	1.49 (1.78)	4.23 (2.33)	3.85	5.72	−1.13 (1.59)	−0.74 (1.13)	−1.87	19 (40)
4 (highest)	0.13 (0.078)	3.13 (1.23)	0.61 (0.91)	3.52 (1.86)	3.26	4.13	−0.47 (0.89)	−0.39 (1.19)	−0.87	8 (17)

Deaths, years lived with disability, and changes are reported per 100,000 persons.
SD, standard deviation; YLD, years lived with disability.

NTD-specific average deaths and YLD (standard deviation [SD]) and their sums for 1990 and 2019, average change in those values, and nations with folic acid fortification for each GDP quartile are summarized in Table 2. Average deaths in 2019 were negatively correlated with increasing GDP quartile and were 3.70 (SD, 3.00), 1.02 (SD, 1.40), 0.36 (SD, 0.26), and 0.13 (SD, 0.078), respectively ($P < 0.0001$; all post hoc comparisons were significant except for comparisons between the second and third and the third and fourth quartiles). Average YLD were also negatively correlated with GDP quartile and were 7.59 (SD, 3.19), 4.29 (SD, 2.35), 3.49 (SD, 1.68), and 3.13 (SD, 1.23), respectively ($P < 0.0001$; post hoc comparisons between the second and third, second and fourth, and third and fourth quartiles were not significant.). Average deaths decreased in each GDP quartile by −5.91 (SD, 4.14), −2.34 (SD, 1.93), −1.13 (SD, 1.59), and −0.47 (SD, 0.89), respectively ($P < 0.0001$; post hoc comparisons between the second and third and third and fourth quartiles were not significant). Likewise, YLD decreased in each quartile by −0.93 (SD, 0.89), −1.14 (SD, 0.75), −0.74 (SD, 1.13), and −0.39 (SD, 1.19), respectively ($P = 0.0035$; the only significant post hoc comparison was between the second and fourth quartiles). The numbers of countries in each per capita GDP quartile with folic acid fortification programs decreased with increasing GDP and were 23 (49%), 21 (44%), 19 (40%), and 8 (17%), respectively ($P = 0.0060$). Figure 1 shows NTD–attributable deaths in 1990 and 2019 and the change from 1990 to 2019 for 191 countries, arranged in order of increasing GDP per capita. Figure 2 shows NTD–attributable YLD in 1990 and 2019 and the change from 1990 to 2019 for 191 countries, arranged in order of increasing GDP per capita.

Table 3 shows NTD-specific average deaths and YLD (SD) and their sums for 1990 and 2019, average change in those values, and

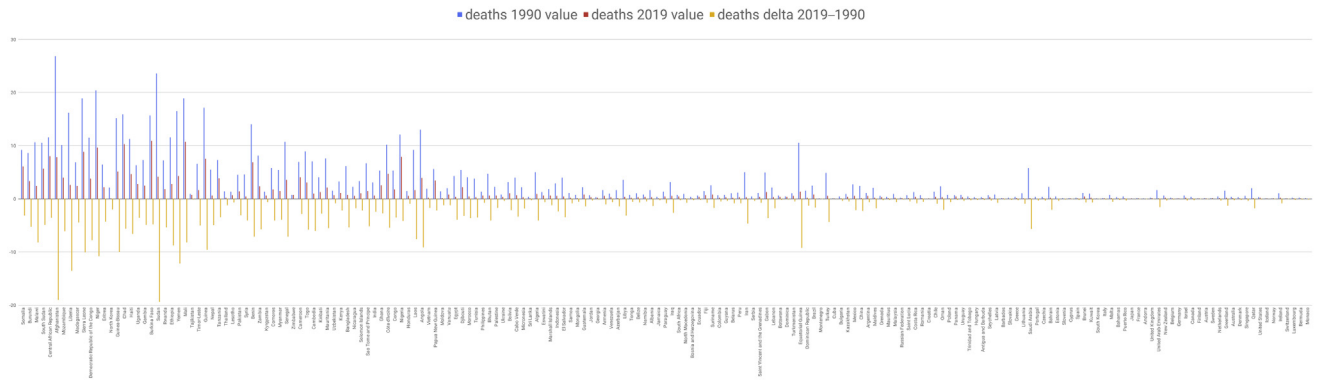

Figure 1. Neural tube defect–attributable deaths in 1990 and 2019 and the change from 1990 to 2019 for 191 countries, arranged in order of increasing gross domestic product per capita.

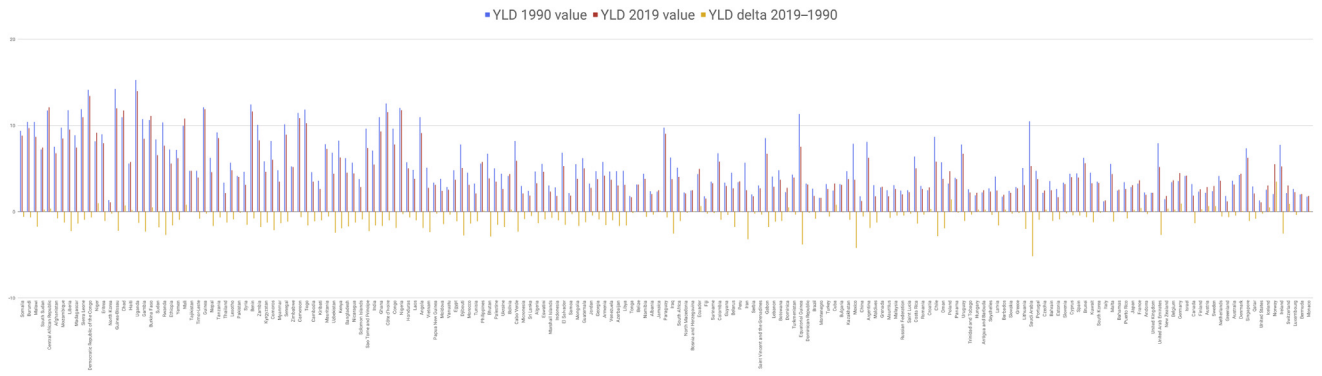

Figure 2. Neural tube defect–attributable years lived with disability in 1990 and 2019 and the change from 1990 to 2019 for 191 countries, arranged in order of increasing gross domestic product per capita.

nations with folic acid fortification for each HAQ index quartile. Average deaths in 2019 were negatively correlated with increasing HAQ index quartile and were 3.73 (SD, 2.95), 1.04 (SD, 1.41), 0.31 (SD, 0.19), and 0.13 (SD, 0.074), respectively ($P < 0.0001$; all post hoc comparisons were significant except for comparisons between the second and third and the third and fourth quartiles). Average YLD in 2019 were also negatively correlated with HAQ index quartile and were 7.67 (SD, 3.28), 4.56 (SD, 2.20), 3.16 (SD, 1.35), 3.10 (SD, 1.14), respectively ($P < 0.0001$; all post hoc comparisons were significant except for between the third and fourth quartiles). The number and percent of countries in each HAQ index quartile with folic acid fortification programs were 27 (57%), 19 (40%), 18 (38%), and 7 (15%), respectively ($P = 0.0003$). Figure 3 shows NTD–attributable deaths in 1990 and 2019 and the change from 1990 to 2019 for 191 countries, arranged in order of increasing HAQ index. Figure 4 shows NTD–attributable YLD in 1990 and 2019 and the change from 1990 to 2019 for 191 countries, arranged in order of increasing HAQ index.

Table 4 shows NTD-specific average deaths and YLD (SD) and their sums for 1990 and 2019, average change in those values, and nations with folic acid fortification for each United Nations geoscheme geographic region. The 10 regions with the greatest average disease burdens, calculated from the sum of average deaths and YLD, from highest to lowest, were Western Africa (15.38), Middle Africa (14.21), Eastern Africa (9.75), South America (5.37), Southern Asia (5.32), Central America (4.94), Central Asia (4.91), Northern Africa (4.76), Southern Africa (4.70), and South-Eastern Asia (4.52). Of the 10 regions (50%) with the highest total disease burden, 5 were African, 3 (30%) were Asian, and 2 (20%) were American ($P = 0.011$). Figure 5 shows NTD–attributable deaths from 1990 to 2019 stratified by World Bank regions. Figure 6 shows NTD–attributable YLD from 1990 to 2019 stratified by World Bank regions.

Table 3. Neural Tube Defect–Specific Average Deaths and Years Lived with Disability and Their Sum for 1990 and 2019, Average Change in Those Values, and Nations with Folic Acid Fortification for Each Healthcare Access and Quality Index Quartile

Healthcare Access and Quality Index Quartile	Average Deaths in 2019, n (SD)	Average YLD in 2019, n (SD)	Average Deaths in 1990, n (SD)	Average YLD in 1990, n (SD)	Deaths + YLD 2019 (n)	Deaths + YLD 1990 (n)	Average Change in Deaths 2019–1990, n (SD)	Average Change in YLD 2019–1990, n (SD)	Average Change in Deaths + YLD 2019–1990	Countries with Folic Acid Fortification, n (%)
1 (lowest)	3.73 (2.95)	7.67 (3.28)	9.25 (5.71)	8.66 (3.36)	11.4	17.91	−5.52 (3.64)	−0.99 (0.99)	−6.51	27 (57)
2	1.04 (1.41)	4.56 (2.20)	3.61 (4.37)	5.45 (2.56)	5.60	9.06	−2.57 (3.37)	−0.89 (0.84)	−3.46	19 (40)
3	0.31 (0.19)	3.16 (1.35)	1.57 (1.35)	4.20 (1.92)	3.47	5.77	−1.26 (1.24)	−1.04 (0.98)	−2.30	18 (38)
4 (highest)	0.13 (0.074)	3.10 (1.14)	0.63 (0.95)	3.40 (1.71)	3.23	4.03	−0.49 (0.92)	−0.30 (1.17)	−0.80	7 (15)

Deaths, years lived with disability, and changes are reported per 100,000 persons.
SD, standard deviation; YLD, years lived with disability.

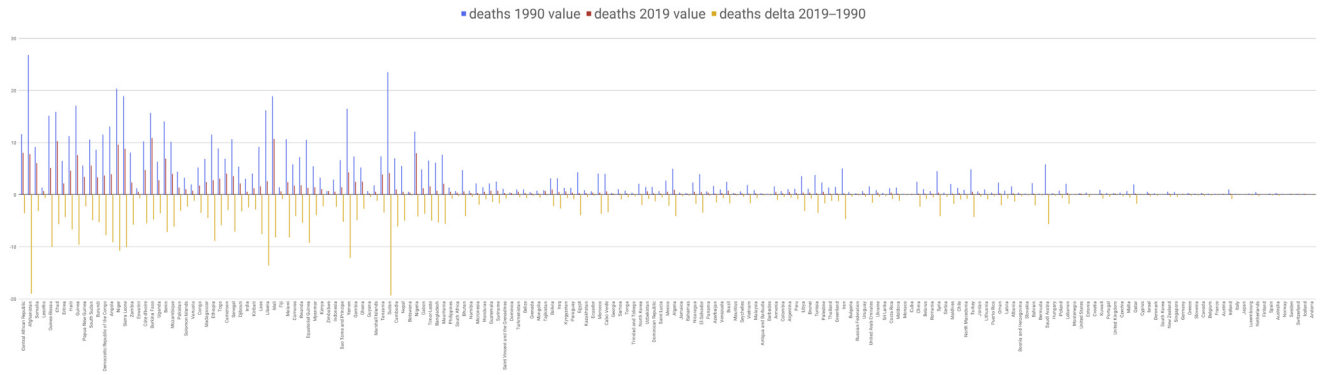

Figure 3. Neural tube defect–attributable deaths in 1990 and 2019 and the change from 1990 to 2019 for 191 countries, arranged in order of increasing Healthcare Access and Quality Index.

Table 5 shows NTD-specific average deaths and YLD (SD) and their sums for 1990 and 2019, average change in those values, and countries with folic acid fortification programs overall and for each per capita GDP quartile. Average deaths were higher in the groups with programs compared with the group without them (2.00 vs. 0.87; P = 0.0005). Average YLD were also higher in countries with folic acid fortification programs compared with countries without them (5.75 vs. 3.94; P < 0.0001) According to the FFI, 71 of 191 nations (37%) had folic acid fortification programs. From 1990 to 2019, average deaths decreased more in nations with fortification programs (−3.45 vs. −1.85; P = 0008), as did YLD (−1.09 vs. −0.63; P = 0.0034).

DISCUSSION

Epidemiology and Prevention

Our results showed that low and middle-income nations and those with lower-quality health care shared a disproportionately high burden of disease caused by NTDs. Nations in Africa and Asia were the most affected. In contrast, nations in North America, Australia, the Caribbean, Latin America, and Europe had smaller disease burdens. These results are similar to findings in the existing literature: in 2015, Blencowe et al.,[20] using data from literature searches and online birth defect registries (and with the application of proprietary meta-analyses) found the highest number of NTD-affected birth outcomes in nations in Asia and Africa and the lowest in Europe, Latin America and the Caribbean, and North America. These investigators also found a relatively high burden in the region that they termed Australasia and Oceania.

It is reasonable to hypothesize that access to folic acid–fortified foods is a main driving factor in the observed pattern of NTD distribution, with women of childbearing age in low and middle-income nations being more often exposed to folate deficiency. The link between these conditions and poor folic acid intake is well established, and the effects of folic acid fortification programs have been well characterized.[4,21]

It is likely that prenatal care also shapes the pattern. Many patients in wealthier nations with higher-quality health care systems with access to screening modalities such as ultrasonography can and do choose to abort fetuses with NTDs.[20,22,23] This factor

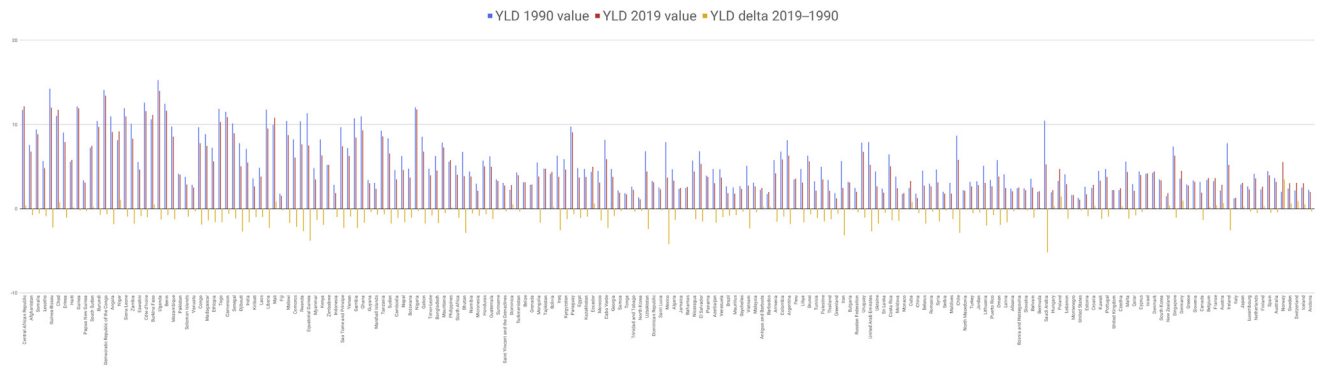

Figure 4. Neural tube defect–attributable years lived with disability in 1990 and 2019 and the change from 1990 to 2019 for 191 countries, arranged in order of increasing Healthcare Access and Quality Index.

Table 4. Neural Tube Defect–Specific Average Deaths and Years Lived with Disability and Their Sum for 1990 and 2019, Average Change in Those Values, and Nations with Folic Acid Fortification for Each United Nations Geoscheme Geographic Region

United Nations Geoscheme Geographic Region	Average Deaths in 2019, n (SD)	Average YLD in 2019, n (SD)	Average Deaths in 1990, n (SD)	Average YLD in 1990, n (SD)	Deaths + YLD 2019 (n)	Deaths + YLD 1990 (n)	Average Change in Deaths 2019–1990, n (SD)	Average Change in YLD 2019–1990, n (SD)	Average Change in Deaths + YLD 2019–1990	Countries with Folic Acid Fortification, n (%)
Australia and New Zealand	0.19 (0.02)	2.50 (0.67)	0.48 (0.087)	2.55 (1.07)	2.69	3.03	−0.29 (0.065)	−0.048 (0.41)	−0.34	1 (50)
Caribbean	0.54 (1.18)	2.87 (0.91)	1.37 (2.88)	2.83 (0.91)	3.41	4.20	−0.83 (1.71)	0.041 (0.39)	−0.79	2 (15)
Central America	0.52 (0.13)	4.42 (0.74)	1.96 (1.01)	5.73 (1.44)	4.94	7.69	−1.42 (0.97)	−1.30 (1.23)	−2.75	8 (100)
Central Asia	0.60 (0.13)	4.31 (0.37)	1.13 (0.25)	5.29 (0.92)	4.91	6.42	−0.52 (0.23)	−0.99 (0.84)	−1.51	2 (40)
Eastern Africa	2.56 (1.57)	7.19 (2.68)	6.64 (3.38)	8.44 (2.86)	9.75	15.08	−4.08 (2.38)	−1.25 (0.82)	−5.33	10 (56)
Eastern Asia	0.13 (0.056)	2.52 (1.13)	1.09 (1.02)	2.99 (1.46)	2.65	4.08	−0.96 (0.98)	−0.47 (0.64)	−1.43	1 (20)
Eastern Europe	0.16 (0.097)	2.76 (0.72)	0.61 (0.37)	3.15 (0.82)	2.92	3.76	−0.45 (0.32)	−0.39 (0.92)	−0.84	1 (9)
Melanesia	1.49 (1.12)	2.51 (0.60)	3.09 (1.60)	2.95 (0.75)	4.00	6.04	−1.60 (0.63)	−0.43 (0.28)	−2.04	2 (50)
Micronesia	0.73 (0.39)	2.36 (0.22)	2.70 (0.98)	3.21 (0.28)	3.09	5.91	−1.97 (0.66)	−0.85 (0.98)	−2.82	1 (33)
Middle Africa	4.34 (3.06)	9.87 (2.29)	10.36 (4.10)	11.07 (1.46)	14.21	21.43	−6.03 (2.53)	−1.20 (1.31)	−7.22	2 (20)
Northern Africa	1.11 (1.39)	3.65 (1.38)	7.39 (7.25)	5.06 (1.57)	4.76	12.45	−6.28 (5.87)	−1.41 (0.25)	−7.69	1 (17)
Northern America	0.18 (0.071)	1.56 (0.42)	0.61 (0.54)	2.10 (0.69)	1.74	2.71	−0.43 (0.49)	−0.53 (0.52)	−0.97	2 (50)
Northern Europe	0.12 (0.051)	3.32 (1.22)	0.44 (0.36)	3.52 (1.73)	3.44	3.96	−0.32 (0.36)	−0.20 (1.62)	−0.52	0 (0)
Polynesia	0.25 (0.013)	1.79 (0.097)	0.93 (0.15)	2.00 (0.15)	2.04	2.93	−0.69 (0.16)	−0.21 (0.57)	−0.89	0 (0)
South America	0.50 (0.23)	4.87 (1.90)	1.41 (0.81)	5.60 (2.35)	5.37	7.01	−0.91 (0.59)	−0.74 (0.91)	−1.64	9 (75)
South-Eastern Asia	0.73 (0.56)	3.79 (1.43)	3.49 (2.88)	4.78 (1.29)	4.52	8.27	−2.76 (2.39)	−0.99 (0.59)	−3.75	3 (27)
Southern Africa	0.51 (0.11)	4.19 (0.44)	0.95 (0.29)	5.10 (0.47)	4.70	6.05	−0.44 (0.20)	−0.91 (0.18)	−1.35	2 (40)
Southern Asia	1.38 (2.31)	3.94 (1.57)	6.47 (7.41)	5.45 (1.72)	5.32	11.92	−5.08 (5.17)	−1.51 (0.96)	−6.60	4 (44)
Southern Europe	0.11 (0.074)	2.58 (0.95)	0.46 (0.43)	2.85 (1.28)	2.79	3.31	−0.36 (0.37)	−0.27 (0.41)	−0.52	0 (0)
Western Africa	5.46 (3.30)	9.92 (1.72)	12.37 (4.99)	10.90 (1.76)	15.38	23.27	−6.91 (2.97)	−0.98 (1.09)	−7.89	11 (73)
Western Asia	0.54 (0.93)	3.68 (1.03)	2.97 (3.62)	5.14 (1.84)	4.22	8.11	−2.43 (2.79)	−1.46 (1.14)	−3.89	9 (50)
Western Europe	0.10 (0.034)	3.18 (0.79)	0.21 (0.11)	2.89 (0.77)	3.28	3.10	−0.10 (0.10)	0.29 (0.52)	0.18	0 (0)

Deaths, years lived with disability, and changes are reported per 100,000 persons.
SD, standard deviation; YLD, years lived with disability.

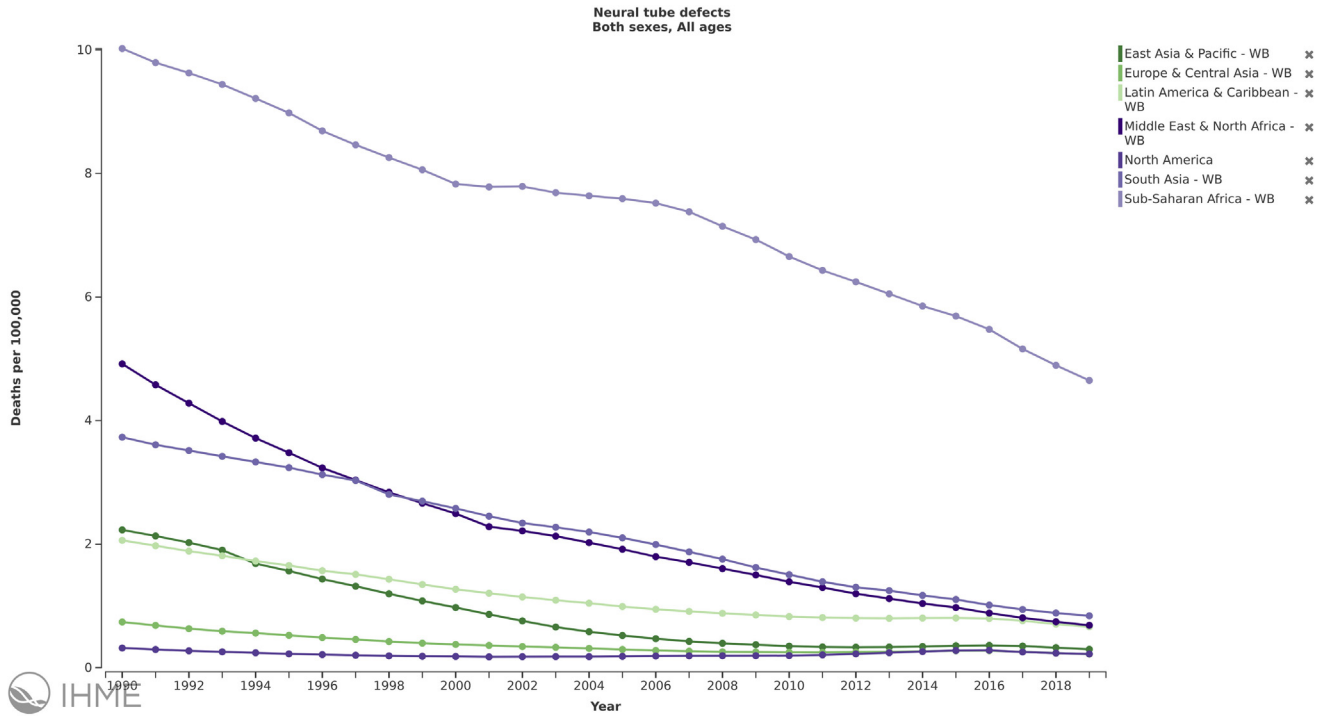

Figure 5. Neural tube defect–attributable deaths from 1990 to 2019 stratified by World Bank regions.

would reduce the burden of disease caused by NTDs in such nations.

We identified changes in the global burden of disease caused by NTDs between 1990 and 2019, but we were unable to infer any causality because we are working with heterogeneous survey data. Nevertheless, deaths decreased in nearly all nations during that time frame. It is reassuring that the greatest decreases occurred in the bottom 2 quartiles for GDP and HAQ index, in which both the largest disease burden and most folic acid fortification programs are concentrated. These findings seemingly support the claim that many NTDs each year are now prevented through folic acid fortification programs.[1,4] Nevertheless, some of the greatest decreases in the burden of disease caused by NTDs were seen in nations without folic acid fortification programs. Sudan, the nation with the greatest change in deaths, did not have a folic acid fortification program, nor did 6 other nations among 20 leaders for this metric. It is possible that other general health care improvements led to reduced burden of NTDs in these nations. Although our data do not represent a sample, the fact that this decrease in deaths was not statistically significant when stratified by quartile supports the notion that reducing the global burden of NTDs is more complicated than simply fortifying foods with folic acid. The significance of changes in YLD was also difficult to interpret. That YLD have decreased in about half of the world's nations may reflect a decrease in NTD incidence or an increase in successful NTD repair and improved quality of life in more developed nations.

Treatment

Widespread attention has been given to efforts focused on preventing NTDs through ensuring adequate folic acid supplementation among women trying to conceive.[21] The neurosurgical community has been called on to further aid these efforts.[3] Nevertheless, as shown by the results of our study and others before it, NTDs continue to cause large disease burdens, even in nations with folic acid fortification programs, improving health care systems, and increasing standards of living. This finding may point to failures of fortification programs to reach the entire population for whom they are implemented. In addition, persistent disease burdens despite adequate folic acid intake reflect a multifactorial disease process that includes NTDs that are not sensitive to folate[6,9-11]: although folate deficiency is among the most established causes of NTD, some evidence suggests that fewer than half of all NTDs are attributable to known risk factors.[5] Sufficient access to definitive neurosurgical care is thus desperately needed in all nations with high NTD disease burdens.

The neurosurgical treatments of NTDs and their sequelae require advanced training on the part of operating physicians and demand access to operative suites and postsurgical intensive care units. Spina bifida is often treated with surgical closure and coverage of the lesion and may require extensive follow-up and multiple additional surgeries as the patient grows to treat associated diseases such as spinal cord tethering and hydrocephalus.[18] Chiari malformations, especially type II, often occur together with

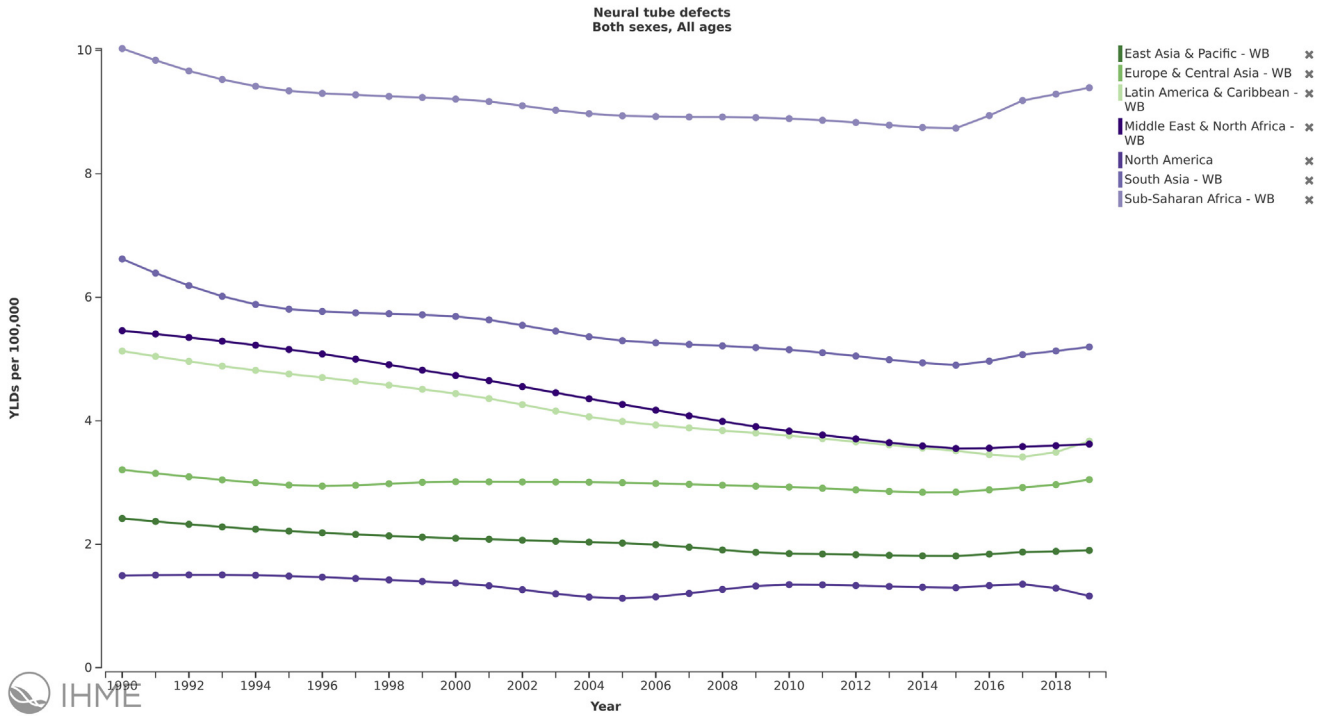

Figure 6. Neural tube defect–attributable years lived with disability from 1990 to 2019 stratified by World Bank regions.

spina bifida and may require surgical treatment.[24] Likewise, the treatment of encephaloceles involves surgical reduction of herniation, dural closure, and coverage of the defect. Craniofacial bone abnormalities caused by the herniation may also require repair. Increasingly, best evidence suggests that repair of open defects in utero may lead to improved outcomes compared with postnatal repair for a variety of reasons.[25-27]

With increasing improvements in neurosurgical care for NTDs, the requirement for timely access to such care will only become more important for providing definitive treatment. This care is often inaccessible, deficient, or even absent in the low-income nations highly affected by NTDs, where it is most needed.[28-30] It seems that access to neurosurgical care is a luxury that few enjoy globally. Studies suggest that a shortage of neurosurgeons exists even in high-income nations such as the United States, especially in rural areas.[31] Low and middle-income nations have fewer neurosurgeons per capita, in addition to lacking general health care infrastructure and ancillary services required for effective repair and optimal perioperative treatment of NTDs.[28-30,32] Many low and middle-income nations may also prefer that their national medical expenditures be allocated to more cost-efficient treatments such as preventing communicable diseases.

Neurosurgical Infrastructure

The worldwide shortage of neurosurgeons and its likely impact on access to neurosurgical care for patients with NTD in low and middle-income nations was characterized in separate reports by Dewan et al.[32] and Mukhopadhyay et al.[33] These researchers investigated the global neurosurgical workforce through original surveys, literature reviews, and statistical modeling. Dewan et al.[32] pointed out particularly worrisome geographic treatment gaps for neurosurgical cases in Africa and South-East Asia, which correspond to the regions we found to have the highest burden of disease caused by NTDs. This group estimated that 23,300 additional neurosurgeons were needed to address an unmet need of 5 million cases per year in low and middle-income nations. Mukhopadhyay et al. concluded that in 161 nations (most of which were low or middle-income) there was less than 1 neurosurgeon per 100,000 people. This group determined that the 2 world regions with the fewest neurosurgeons per capita were Africa and South-East Asia. As an example of a particularly dire situation, these investigators point to the Democratic Republic of the Congo (22nd most deaths and second-highest YLD caused by NTDs in our analysis): in this nation, 4 neurosurgeons were available to serve nearly 75 million people.[33]

The global neurosurgical community should both be aware of and help address disparities in access to neurosurgical care for patients with NTD that exist among different income groups and geographic regions. A focus on sustainable and low-cost interventions would be most ideal. Examples of such efforts might include helping to facilitate an increase in the number of neurosurgeons per capita in the nations that need them most by founding and/or supporting local training and residency programs. Likewise, surgeon exchange programs could be a relatively

Table 5. Neural Tube Defect—Specific Average Deaths and Years Lived with Disability and Their Sum for 1990 and 2019, Average Change in Those Values, and Nations with Folic Acid Fortification for Each per Capita GDP Quartile

Gross Domestic Product per Capita Quartile	Folic Acid Fortification Binary	Number of Countries, n (%)	Average Deaths in 2019, n (SD)	Average YLD in 2019, n (SD)	Average Deaths in 1990, n (SD)	Average YLD in 1990, n (SD)	Deaths + YLD 2019	Deaths + YLD 1990	Average Change in Deaths 2019—1990, n (SD)	Average Change in YLD 2019—1990, n (SD)	Average Change in Deaths + YLD 2019—1990
All	Present	71 (37)	2.00 (2.73)	5.75 (3.16)	5.45 (5.90)	6.83 (3.27)	7.75	12.28	−3.45 (3.66)	−1.09 (1.05)	−4.53
	Absent	120 (63)	0.87 (1.61)	3.94 (2.38)	2.72 (3.97)	4.57 (2.79)	4.81	7.29	−1.85 (2.76)	−0.63 (1.00)	−2.48
1 (lowest)	Present	23 (49)	4.56 (3.15)	5.46 (1.79)	11.77 (6.09)	9.46 (2.78)	10.02	21.23	−7.21 (4.04)	−0.90 (0.88)	−11.21
	Absent	24 (51)	2.88 (2.57)	4.27 (2.04)	7.54 (5.39)	7.61 (3.24)	7.15	15.15	−4.66 (3.85)	−0.95 (0.90)	−8.00
2	Present	21 (44)	1.32 (1.80)	3.25 (1.70)	3.69 (2.84)	6.21 (2.73)	4.57	9.90	−2.37 (1.40)	−1.20 (0.71)	−5.33
	Absent	27 (56)	0.78 (0.92)	2.43 (1.20)	3.11 (2.95)	4.84 (2.37)	3.21	7.95	−2.32 (2.25)	−1.10 (0.78)	−4.74
3	Present	19 (40)	0.43 (0.16)	2.83 (1.23)	1.34 (0.79)	5.24 (2.38)	3.26	6.58	−0.91 (0.73)	−0.96 (1.20)	−3.32
	Absent	29 (60)	0.32 (0.31)	1.95 (0.83)	1.59 (2.20)	3.57 (2.03)	2.27	5.16	−1.27 (1.95)	−0.60 (1.07)	−2.89
4 (highest)	Present	8 (17)	0.18 (0.048)	2.03 (0.91)	1.72 (1.77)	4.69 (2.81)	2.21	6.41	−1.54 (1.72)	−1.63 (1.52)	−4.20
	Absent	40 (83)	0.12 (0.079)	2.08 (0.80)	0.38 (0.33)	3.29 (1.50)	2.20	3.67	−0.26 (0.29)	−0.15 (0.93)	−1.47

Deaths, years lived with disability, and changes are reported per 100,000 persons.
SD, standard deviation; YLD, years lived with disability.

low-cost way to redistribute neurosurgical skill sets to help local surgeons address the high NTD disease burdens that already exist. Medical mission trips and charitable efforts should recognize the burden of disease caused by neurosurgical diseases such as NTDs and should coordinate the delivery of neurosurgical care to where it is lacking most to maximize use of limited resources. Sustainability is crucial for any such programs, because patients with NTD have many complications, and their disabilities cannot be removed. Short-term trips may not make much of a difference unless there is year-round support.

Socioeconomic Complexities and Limitations

Although neurosurgeons can provide treatment to address spina bifida and hydrocephalus, multidisciplinary care required to deal with these complex disease states places a large burden on patients, families, and communities in regions in which adequate infrastructure, including affordable transportation to medical centers, may not be present for such needs. Furthermore, treatment of children with NTDs necessitates treatment by urologists, orthopedists, therapists, and physiatrists, who are in nearly as short supply as neurosurgeons in some of the nations most affected. Addressing cost-effectiveness and health disparities for NTDs requires a host of complex geopolitical issues to be addressed. Any direct efforts of neurosurgeons to surgeon exchange programs must incorporate models for alignment, sustainability, education, and broad networks of multidisciplinary institutional support.

Our study has several limitations. For instance, regarding our data source, the current GBD database iteration does not allow for resolution of subtypes of NTDs. Thus, we are unable to obtain information about the proportion of disease burden caused by spina bifida, encephalocele, or anencephaly. In addition, GBD data come from a variety of sources, and it is difficult to determine which NTDs were counted in each nation. For example, in lower-income nations in which women may not have access to medical care, stillbirths caused by NTDs might not be reported, and health conditions in general may be underreported in low and middle-income nations. Conversely, increased rates of elective abortions of NTDs in wealthier nations may cause a different pattern of morbidity and mortality reporting in these nations that does not reflect natural history. The data from each source that we used are made publicly available on an irregular schedule. We were not able to find any recent year that contained complete data on our outcomes of interest. Therefore, all data were selected from the most recent year for which complete data were available.

Our ability to examine the impact of folic acid fortification programs was limited by the nature of our data as a survey. Furthermore, the FFI publishes only prevalence data, and we cannot ascertain when particular programs went into effect or how successful they were. More in-depth analyses have been performed on the effects of fortification programs that used estimates of a nation's actual per capita consumption of fortified products.[1] Looking solely at which nations have fortification programs, as we did, is not sufficient to examine their impact in granular detail. Our inclusion of FFI data here is intended to show the multifactorial nature and pervasiveness of NTDs despite optimal primary prevention in many nations.

CONCLUSIONS

Neurosurgeons provide definitive treatment of NTDs. Our research shows that the burden of NTDs disproportionately affects low and middle-income nations. These nations have the most limited access to neurosurgical care. Although widespread attention has been given to preventing NTDs such as through folic acid fortification programs, NTDs continue to occur and cause significant disease burdens despite those programs. It is therefore appropriate for the medical and public health communities to focus on improving access to neurosurgical care for these conditions. Transference of surgical skills through surgeon exchange programs and efforts to establish or improve self-sustaining neurosurgical infrastructure in lower and middle-income nations is a fast and cost-effective way to reduce health disparities caused by NTDs such as spina bifida, encephalocele, and anencephaly.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Alex Yacob: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing - original draft, Visualization. **Christopher J. Carr:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration. **Jake Foote:** Validation, Investigation, Writing - review & editing. **Tyler Scullen:** Methodology, Writing - review & editing. **Cassidy Werner:** Investigation, Resources, Data curation, Writing - review & editing. **Mansour Mathkour:** Conceptualization, Methodology, Writing - review & editing, Project administration. **Cuong J. Bui:** Writing - review & editing, Supervision. **Aaron S. Dumont:** Conceptualization, Resources, Writing - review & editing, Supervision, Project administration.

REFERENCES

1. Arth A, Kancherla V, Pachón H, Zimmerman S, Johnson Q, Oakley GP Jr. A 2015 global update on folic acid-preventable spina bifida and anencephaly. *Birth Defects Res A Clin Mol Teratol*. 2016;106:520-529.
2. Botto LD, Moore CA, Khoury MJ, Erickson JD. Neural-tube defects. *N Engl J Med*. 1999;341:1509-1519.
3. Estevez-Ordonez D, Davis MC, Hopson B, et al. Reducing inequities in preventable neural tube defects: the critical and underutilized role of neurosurgical advocacy for folate fortification. *Neurosurg Focus*. 2018;45:E20.
4. Kancherla V, Wagh K, Johnson Q, Oakley GP Jr. A 2017 global update on folic acid-preventable spina bifida and anencephaly. *Birth Defects Res*. 2018;110:1139-1147.
5. Agopian AJ, Tinker SC, Lupo PJ, Canfield MA, Mitchell LE, National Birth Defects Prevention Study. Proportion of neural tube defects attributable to known risk factors. *Birth Defects Res A Clin Mol Teratol*. 2013;97:42-46.
6. Correa A, Botto L, Liu Y, Mulinare J, Erickson JD. Do multivitamin supplements attenuate the risk for diabetes-associated birth defects? *Pediatrics*. 2003;111:1146-1151.
7. Crider KS, Devine O, Hao L, et al. Population red blood cell folate concentrations for prevention of neural tube defects: Bayesian model. *BMJ*. 2014;349:g4554.
8. Greene ND, Copp AJ. Neural tube defects. *Annu Rev Neurosci*. 2014;37:221-242.
9. Missmer SA, Suarez L, Felkner M, et al. Exposure to fumonisins and the occurrence of neural tube

defects along the Texas-Mexico border. *Environ Health Perspect*. 2006;114:237-241.

10. Moretti ME, Bar-Oz B, Fried S, Koren G. Maternal hyperthermia and the risk for neural tube defects in offspring: systematic review and meta-analysis. *Epidemiology*. 2005;16:216-219.

11. Wlodarczyk BJ, Palacios AM, George TM, Finnell RH. Antiepileptic drugs and pregnancy outcomes. *Am J Med Genet A*. 2012;158A:2071-2090.

12. Greene ND, Stanier P, Copp AJ. Genetics of human neural tube defects. *Hum Mol Genet*. 2009;18: R113-R129.

13. Harris MJ, Juriloff DM. Mouse mutants with neural tube closure defects and their role in understanding human neural tube defects. *Birth Defects Res A Clin Mol Teratol*. 2007;79:187-210.

14. Etheredge AJ, Finnell RH, Carmichael SL, et al. Maternal and infant gene-folate interactions and the risk of neural tube defects. *Am J Med Genet A*. 2012;158A:2439-2446.

15. Shaw GM, Lu W, Zhu H, et al. 118 SNPs of folate-related genes and risks of spina bifida and conotruncal heart defects. *BMC Med Genet*. 2009;10:49.

16. Noor RA, Abioye AI, Ulenga N, et al. Large-scale wheat flour folic acid fortification program increases plasma folate levels among women of reproductive age in urban Tanzania. *PLoS One*. 2017;12:e0182099.

17. Yi Y, Lindemann M, Colligs A, Snowball C. Economic burden of neural tube defects and impact of prevention with folic acid: a literature review. *Eur J Pediatr*. 2011;170:1391-1400.

18. Sandler AD. Children with spina bifida: key clinical issues. *Pediatr Clin North Am*. 2010;57:879-892.

19. Sandler A, Goodrich J. Encephaloceles, meningoceles, and cranial dermal sinus tracts. In: Win H, ed. *Youmans and Winn Neurological Surgery*. 7th ed. Philadelphia, PA: Elsevier; 2017:1506-1517.

20. Blencowe H, Kancherla V, Moorthie S, Darlison MW, Modell B. Estimates of global and regional prevalence of neural tube defects for 2015: a systematic analysis. *Ann N Y Acad Sci*. 2018; 1414:31-46.

21. Castillo-Lancellotti C, Tur JA, Uauy R. Impact of folic acid fortification of flour on neural tube defects: a systematic review [published correction appears in Public Health Nutr. 2013 Aug;16(8): 1527]. *Public Health Nutr*. 2013;16:901-911.

22. Domröse CM, Bremer S, Buczek C, et al. Termination of pregnancy after prenatal diagnosis of spina bifida: a German perspective. *Arch Gynecol Obstet*. 2016;294:731-737.

23. Steric M, Stamenkovic JD, Srbinovic L, et al. The outcome and course of pregnancies complicated with fetal neural tube defects. *Clin Exp Obstet Gynecol*. 2015;42:57-61.

24. Copp AJ, Adzick NS, Chitty LS, Fletcher JM, Holmbeck GN, Shaw GM. Spina bifida. *Nat Rev Dis Primers*. 2015;1:15007.

25. Adzick NS, Thom EA, Spong CY, et al. A randomized trial of prenatal versus postnatal repair of myelomeningocele. *N Engl J Med*. 2011; 364:993-1004.

26. Adzick NS. Fetal surgery for spina bifida: past, present, future. *Semin Pediatr Surg*. 2013;22:10-17.

27. Mummareddy N, Dewan MC, Huang A, et al. Intrauterine closure of myelomeningocele is associated with superior long-term quality of life than postnatal closure: a single-center study [published online ahead of print, 2019 May 17]. *J Neurosurg Pediatr*. 2019;24:115-119.

28. Park KB, Johnson WD, Dempsey RJ. Global neurosurgery: the unmet need. *World Neurosurg*. 2016;88:32-35.

29. Punchak M, Mukhopadhyay S, Sachdev S, et al. Neurosurgical care: availability and access in low-income and middle-income countries. *World Neurosurg*. 2018;112:e240-e254.

30. Sader E, Yee P, Hodaie M. Assessing barriers to neurosurgical care in Sub-Saharan Africa: the role of resources and infrastructure. *World Neurosurg*. 2017;98:682-688.e3.

31. Ahmed AK, Duhaime AC, Smith TR. Geographic proximity to specialized pediatric neurosurgical care in the contiguous United States. *J Neurosurg Pediatr*. 2018;21:434-438.

32. Dewan MC, Rattani A, Fieggen G, et al. Global neurosurgery: the current capacity and deficit in the provision of essential neurosurgical care. Executive summary of the Global Neurosurgery Initiative at the Program in Global Surgery and Social Change [e-pub ahead of print]. *J Neurosurg*. 2018:1-10. https://doi.org/10.3171/2017.11.JNS171500.

33. Mukhopadhyay S, Punchak M, Rattani A, et al. The global neurosurgical workforce: a mixed-methods assessment of density and growth [e-pub ahead of print]. *J Neurosurg*. 2019:1-7. https://doi.org/10.3171/2018.10.JNS171723.

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