phg hna toolkit | Congenital Disorders

Background information on Neural Tube Defects and the impact of interventions

This document gives a brief overview about the condition, its epidemiology and specific interventions that may reduce its burden.

What are Neural Tube Defects?

Neural tube defects (NTDs) are complex congenital malformations of the central nervous system (CNS) caused by incomplete closure of the neural tube. They include spina bifida, encephalocoele (e-coele) and anencephaly. Those with anencephaly are stillborn or die shortly after birth; spina bifida and encephalocoele are compatible with life, but most affected infants are likely to have severe physical and mental disabilities. Although the majority of NTDs are non-syndromic, they can also be a feature of some syndromes such as trisomy 13; this document focuses on NTDs that are not part of specific genetic syndromes.

What are the main risk factors?

NTDs are thought to be caused by a combination of genetic and environmental factors. The most common risk factor is maternal folate deficiency; however, the mechanism by which folate prevents NTDs is not known. The risk when a previous child or one of the parents has the condition is 4% to 5%[1]. Rare genetic disorders, maternal diabetes, use of some medications such as folate antagonists e.g. valproic acid or carbamazepine in pregnancy, and other teratogens may also increase the risk of the condition in the offspring.

Global epidemiology

Birth prevalence

According to the Modell Database of Constitutional Congenital Disorders (MGDB), approximately 230,000 or 1.70/1,000 babies with NTD are born alive in the world every year (live birth prevalence). Another 75,000 are stillborn (0.56/1,000 births). Most affected births (in absolute numbers) are in the Asian continent, particularly in the South and East, and a significant proportion are born in Africa. Table 1 shows the birth prevalence by world region,

[1] Milunsky A, Cannick J. Maternal serum screening for neural tube and other defects. In: Milunsky A, Milunsky J, editors. *Genetic Disorders and the Fetus: Diagnosis, Prevention and Treatment*. Wiley-Blackwell; 2010:705-771.

to illustrate a broad global overview; country level estimates can be obtained from the MGDB.

Population prevalence

Approximately 560,000 people in the world live with the condition (population prevalence), with many in South, South East and East Asia and the Middle-East. The population prevalence in each country depends on the country specific population age distribution, proportion of affected pregnancies that are terminated, birth prevalence, retrospective life expectancy, and type and quality of treatment and care, including if and when an aggressive treatment policy was introduced. The population prevalence by age-groups and world regions is shown in Table 2.

Mortality

The condition contributes to around 250,000 deaths per year, about half of these in South Asia. The disease specific mortality estimates by world region and age-groups appear in Table 3.

Disability and quality of life

Improved perinatal, neonatal and neurosurgical care reduces early mortality associated with NTD. Surviving infants have a range of severities from none to severe cognitive and physical disability, depending on the severity of the defect and the impact of postnatal management. They require follow-up and care throughout life to treat complications including infections and possible neurological lesion as well as any associated physical disability or intellectual impairment.

Tables 4a and 4b show an illustration of the expected sequelae of spina bifida and the number of people living with different levels of disability by age-group and region.

Reducing prevalence, morbidity and mortality

Figure 1 illustrates the determinants and interventions for NTD as they relate to key stages in life. The main specific interventions are discussed below.

Interventions before pregnancy

These include the maintenance of good periconception folate nutrition, folic acid food fortification aimed at the whole population, and supplementation in the form of folic acid pills, either to all women or those in the preconception period.

Folic acid fortification of foods is a very effective intervention to reduce the incidence and severity of NTD. Mandatory folic acid fortification of foods could reduce the NTD incidence to 0.5 - 0.9/1,000, with the remaining cases being 'folate resistant'[2]; however this is hard to achieve and is also dependent on the baseline prevalence of the condition. For optimum results, it requires fortification of food staples that are widely consumed across the country or target population. In countries where it has been implemented, the incidence of NTD has been reduced by between 14% and 46%. As of June 2010, just over a quarter of the world population had access to folic acid fortified foods. For country specific data on food fortification go to http://www.sph.emory.edu/wheatflour/index.php.

[2] Wyszynski D (ed). *Neural Tube Defects: From Origin to Treatment*. 2006 Oxford University Press.

Dietary supplementation with folic acid pills, started at least a month before conception and continued until 12 weeks gestation, is very effective at the individual level, but good population coverage is dependent on effective strategies to implement such programme. In optimum circumstances, it may reduce the risk of NTD by 62% (95% CI: 49 - 71)[3].

Interventions during pregnancy

Prenatal care involves screening and diagnosis during pregnancy. This allows planning for a future baby with a congenital disorder or, in places where it is legal and acceptable, may lead to a choice of pregnancy termination. Worldwide, prenatal screening usually has high coverage. However, the quality of the services is variable and often poor, and state funded screening for anomalies is not common practice in many areas with less developed health services. Prenatal screening may involve different methods, for example maternal serum alpha fetoprotein (MSAFP) measurement or fetal ultrasound scan (USS). Confirmation of diagnosis involves ultrasound and less commonly amniocentesis. MSAFP at 16 weeks gestation has been linked with a detection rate of 82% and a false positive rate of 1.6%, but it does not detect closed defects. Anencephaly can be detected by ultrasound from 11 - 12 weeks of gestation; and spina bifida, from 16 weeks or earlier (from 13 weeks) for large defects. The sensitivity of USS in unselected populations has been reported as 98% for anencephaly, but is variable (65 - 90%) for other NTDs.

Interventions after birth

Care of people with a NTD requires a multidisciplinary approach involving both specialists and generalists for surgery, treatment of complications, rehabilitation, and social support. No treatment is available for anencephaly, which often leads to stillbirths or is lethal in the early neonatal period. Life expectancy can be estimated based on quality of care, and improves as care improves. Minimally treated infants with Neural Tube Defects have a very short life span with severe illness. Death after the first year is usually due to meningitis, hydrocephalus or urinary tract infection. Disability and quality of life varies, depending on disease severity, capacity of health services and timeliness and quality of treatment of conditions and their complications. Surgery can improve the survival and quality of life of those with spina bifida and e-coele. However, the outcome of surgery is variable and depends on the severity of the defect and complications during and following the procedure, experience of the surgical team and health and support services infrastructure.

Cost-effectiveness of interventions

Folic acid supplementation and food fortification are among the most cost-effective public health interventions available. Fortification is relatively inexpensive, although costs vary internationally and with time. As an example, in Chile fortifying flour with folic acid has been estimated to save US$11.8 in medical costs for each dollar spent on fortification. If only one to two cases of NTD were prevented in a year (and many more are), this would have recovered the entire annual cost of fortification with folic acid in that year. In the US, folic acid fortification has been estimated to save US$145 million per year in costs for the care of children born with spina bifida. Prenatal screening and diagnosis also tend to be cost-effective interventions. It is important to note that cost-effectiveness of interventions varies geographically. For the economic benefits of food fortification, see the flour fortification

[3] Blencowe H, Cousens S, Modell B, Lawn J. Folic acid to reduce neonatal mortality from neural tube disorders. *Int J Epidemiol* 2010;39 Suppl 1:i110-i121.

initiative website http://www.sph.emory.edu/wheatflour/economicbenefit.php or the following http://www.foodstandards.gov.au/_srcfiles/P295%20Folate%20Fortification%20FFR%20Attach%202%20FINAL.pdf.

In the US, the average lifetime cost for medical treatment, educational services and lost productivity for one individual with spina bifida in 2002 was estimated to be US$635,763[4]. Treatment and care services for individuals with NTDs require a multidisciplinary approach and the availability and cost of these services can have global variations. For cost-effectiveness cut-off points for different regions of the world, go to http://www.who.int/choice/costs/CER_levels/en/index.html, and for costs for specific items by region and county, go to http://www.who.int/choice/costs/en/.

What are the main ethical legal and social issues (ELSI) to consider?

The ethical basis for state intervention

When public health interventions, such as folic acid fortification of foods, are targeted at populations rather than individuals the intrusiveness of the intervention, and any risks associated with it, should be balanced against the likely benefits, particularly if a degree of coercion is involved.

Current evidence suggests folic acid fortification and supplementation are very safe interventions, especially with intake levels of up to 1 mg/day of folic acid. Daily intakes under 5 mg/day are also likely to be safe. Fortification in high-malaria environments still needs to be examined. Caution has been recommended in these areas. This is because iron, which is often combined with folic acid in food fortification, may increase risk of death in malarial areas; and high doses of folic acid may reduce the efficacy of some antimalarials, such as sulfadoxine and pyrimethamine. At the time of writing, there seems to be no evidence that folic acid in doses used for fortification increases the risk of missing a diagnosis of vitamin B12 deficiency and associated neuropathy. Doses up to 1 mg/day have not been associated with clinically significant drug interactions and can be safely used in controlled epilepsy.

Those that oppose fortification programmes argue that such policies deprive competent adults of the chance to make an autonomous choice. This is particularly the case if all potential sources of a particular product are fortified. As some types of food are less amenable to folic acid fortification than others (for example wheat is more easily fortified than rice), and as some people, usually the most isolated and the less well off in society may not have access to fortified products (e.g. by relying on subsistence agriculture or local produced products) the exclusive use of food fortification may lead to an unfair distribution and access to the benefits conferred by the fortified foods.

It is possible to preferentially target those who are planning a future pregnancy, or at risk of becoming pregnant, by providing folic acid supplementation in the form of folic acid pills. However, such programmes may be less accessible to vulnerable groups or those of lower socio-economic class, raising issues of lack of equity in provision of the service.

[4] http://health.utah.gov/birthdefect/defects/neural.html

Access to prenatal screening and termination of pregnancy

Disadvantaged groups may be less likely to have access to prenatal screening and termination services, particularly if, as in many low and middle income countries (LMIC), these services are funded privately.

In many LMIC legal termination of pregnancy is unavailable or severely restricted to cases where it is necessary to protect the woman's life. In some countries access to termination may also depend upon parental or spousal consent. In practice, in many countries, the majority of procedures are offered illegally, often by unqualified practitioners, and may cause substantial physical and psychological harm.

Exercising a parental choice to continue with an affected pregnancy

There is sometimes concern that it may be difficult for mothers who have an affected child identified on screening to choose to proceed with the pregnancy (with the resultant burden that is likely to impose upon themselves, family, health providers and state).

Living with a disability

Those who are born disabled often have a very poor life expectancy, especially in LMIC. This is due to a combination of factors: lack of access to relevant health and social services compounded by social disadvantages such as poverty and poor education. Affected individuals may experience stigma, discrimination and psychological difficulties.

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RELATED TOPICS

Preconception care and screening

Prenatal care and screening

Newborn screening

Table 1: Estimates for the birth prevalence rates of NTD by GBD world region, 2005 (source: Modell 2010)

	Estimated rates		Estimated stillbirths			Estimated live births		
GBD Region	**Still births /1,000**	**Live births /1,000**	**Anen-cephaly**	**Sp bif or E'cele**	**Total NTD**	**Anen-cephaly**	**Sp bif or E'cele**	**Total NTD**
Sub-Saharan Africa, Central	0.32	0.94	988	261	1,249	988	2,703	3,692
Sub-Saharan Africa, East	0.33	0.96	3,125	825	3,950	3,125	8,551	11,676
Sub-Saharan Africa, South	0.35	1.04	456	123	579	456	1,271	1,728
Sub-Saharan Africa, West	0.39	1.15	3,611	953	4,564	3,611	9,879	13,490
Middle East	0.55	1.64	2,762	741	3,503	2,762	7,677	10,439
North Africa	0.51	1.55	1,433	397	1,830	1,433	4,112	5,545
Caribbean	0.32	0.96	182	50	232	182	517	698
Latin America, Andean	0.31	0.93	294	78	372	294	805	1,099
Latin America, Central	0.33	0.96	1,254	331	1,585	1,254	3,431	4,686
Latin America, Southern	0.22	0.66	176	46	222	176	481	656
Latin America, Tropical	0.38	1.13	1,185	313	1,498	1,185	3,243	4,428
North America, High Income	0.10	0.36	311	127	438	311	1,315	1,626
Asia Pacific, High Income	0.12	0.41	147	52	199	147	537	684
Asia Southeast	0.30	0.88	2,772	734	3,506	2,772	7,606	10,378
Asia, Central	0.50	1.46	600	158	758	600	1,641	2,240
Asia, East	0.66	2.01	9,173	2,553	11,727	9,173	26,462	35,636
Asia, South	1.03	3.12	29,794	8,168	37,962	29,794	84,646	114,440
Europe, Central	0.22	0.70	193	61	254	193	630	823
Europe, Eastern	0.14	0.51	221	83	304	221	856	1,077
Europe, Western	0.03	0.22	39	84	123	39	874	913
Australasia	0.10	0.47	18	12	30	18	126	144
Oceania	0.38	1.12	89	23	112	89	243	332
World	0.56	1.70	58,825	16,173	74,997	58,825	167,607	226,432

Table 2: Estimated number and age distribution of people living with NTD by GBD world region, 2005 (source: Modell, 2010)

GBD Region	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	Total living with NTD
Sub-Saharan Africa, Central	540	396	227	134	59	7	3	2	1	0	0	1,369
Sub-Saharan Africa, East	5,720	4,540	2,217	1,272	631	366	214	124	60	8	0	15,151
Sub-Saharan Africa, South	1,067	960	806	719	616	524	339	225	48	7	0	5,310
Sub-Saharan Africa, West	4,309	3,482	2,392	607	288	76	42	23	11	1	0	11,231
Middle East	10,629	11,007	11,825	9,900	7,414	5,350	3,110	992	483	63	0	60,772
North Africa	4,141	3,566	3,671	2,852	1,959	1,389	849	523	248	32	0	19,230
Caribbean	706	514	366	333	271	245	140	68	32	4	0	2,677
Latin America, Andean	1,578	1,526	1,447	669	346	293	176	105	50	7	0	6,197
Latin America, Central	6,490	6,542	6,308	2,976	1,569	1,316	800	483	232	30	0	26,745
Latin America, Southern	1,194	1,212	1,214	750	511	319	134	83	45	6	0	5,468
Latin America, Tropical	6,784	6,248	6,082	3,126	1,636	1,315	837	545	273	35	0	26,880
North America, High Income	4,820	4,747	5,119	4,978	5,250	4,675	3,516	3,173	205	31	0	36,514
Asia Pacific, High Income	1,914	2,020	2,015	2,284	2,235	2,029	1,705	1,275	103	15	0	15,593
Asia Southeast	23,943	19,352	16,569	8,759	2,966	2,378	1,520	949	466	62	0	76,963
Asia, Central Total	934	961	1,172	1,033	76	0	0	0	0	0	0	4,176
Asia, East	14,750	18,346	24,846	19,048	1,514	0	0	0	0	0	0	78,504
Asia, South	32,189	31,374	31,307	26,671	7,856	1,273	783	471	224	30	0	132,176
Europe, Central	2,317	1,058	1,527	1,656	1,663	924	308	187	105	19	0	9,763
Europe, Eastern	428	495	711	833	775	643	415	268	182	28	0	4,779
Europe, Western	1,671	2,136	2,501	2,831	3,553	3,211	2,644	2,594	173	24	0	21,338
Australasia	300	343	406	451	442	394	373	275	20	3	0	3,008
Oceania	93	81	96	81	20	11	7	4	2	0	0	396
World	126,519	120,907	122,821	91,963	41,648	26,736	17,916	12,367	2,962	404	0	564,243

Table 3: Excess deaths due to NTD by age group and GBD world region, 2005 (source: Modell, 2010)

GBD Region	Under-5 deaths			Later deaths by 5 year age group									Total deaths 2005	Total under-5 deaths	Total later deaths
	<1 month	1-11 months	1-4 yr	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49			
Sub-Saharan Africa, Central	3,000	1,031	60	9	2	1	1	0	0	0	0	0	4,104	4,092	12
Sub-Saharan Africa, East	9,302	3,096	285	110	28	14	8	5	3	4	1	0	12,855	12,683	172
Sub-Saharan Africa, South	1,352	444	52	25	13	9	8	7	4	8	1	0	1,923	1,849	74
Sub-Saharan Africa, West	10,935	3,819	234	74	19	6	3	1	1	1	0	0	15,093	14,988	105
Middle East	7,989	2,549	366	251	198	128	99	77	41	33	6	2	11,738	10,904	834
North Africa	4,193	1,365	211	91	61	37	27	20	11	17	3	1	6,037	5,768	269
Caribbean	535	175	22	11	6	5	5	6	3	2	0	0	771	732	39
Latin America, Andean	799	214	59	27	24	10	6	8	4	3	1	0	1,156	1,072	84
Latin America, Central	3,418	927	249	119	106	46	26	34	19	15	3	1	4,964	4,594	370
Latin America, Southern	459	109	33	20	24	14	12	11	4	3	1	0	690	602	89
Latin America, Tropical	3,194	835	248	110	102	49	28	36	20	17	4	1	4,646	4,276	369
North America, High Income	700	79	39	71	138	110	137	215	141	89	4	2	1,724	818	906
Asia Pacific, High Income	325	32	16	30	54	50	58	93	68	36	2	1	767	374	393
Asia Southeast	7,584	2,101	465	348	296	138	47	55	31	31	7	2	11,105	10,150	955
Asia, Central	1,771	587	64	25	16	12	1	0	0	0	0	0	2,475	2,422	53
Asia, East	27,038	8,946	1,310	496	413	232	20	0	0	0	0	0	38,455	37,294	1,161
Asia, South	91,331	33,473	2,272	696	299	270	73	12	7	17	2	0	128,453	127,076	1,377
Europe, Central	507	122	38	17	37	34	41	37	9	6	2	1	850	667	183
Europe, Eastern	650	209	62	9	13	14	14	18	11	8	3	1	1,012	921	91
Europe, Western	130	52	26	32	68	62	92	148	106	73	3	2	794	209	585
Australasia	43	8	4	5	11	10	12	18	15	8	0	0	133	54	79
Oceania	259	84	11	2	1	1	0	0	0	0	0	0	358	354	5
World	175,514	60,257	6,126	1,929	1,253	716	803	498	370	43	16	0	247,525	241,897	5,628

Table 4a: Sequelae for spina bifida (Source: Modell 2010)

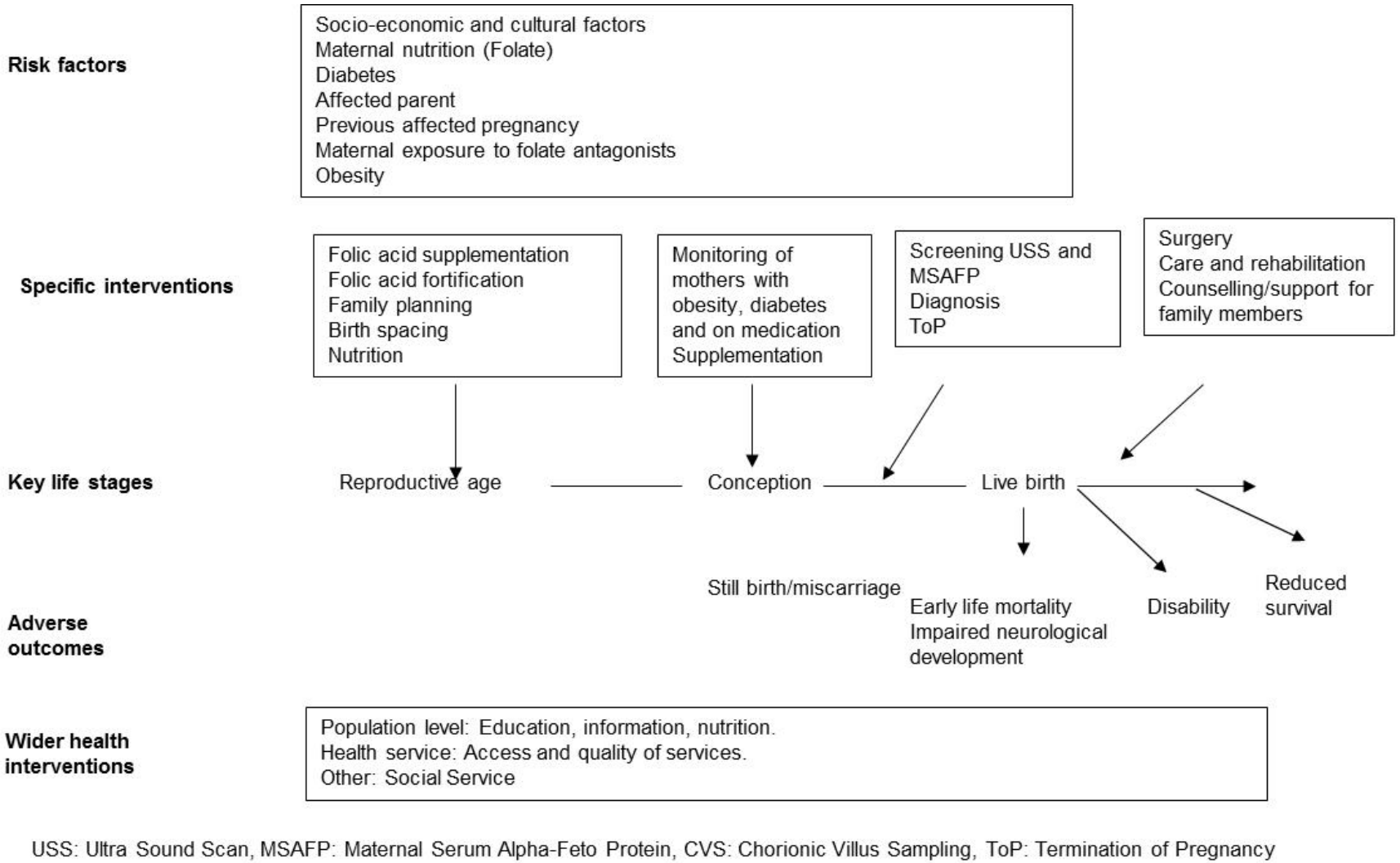
Sequelae group	Sequelae	% of patients
1	Severe disability	37
2	Incontinence, wheelchair	14
3	Wheelchair only	19
4	Problems with mobility and continence	30

Table 4b: Estimates of total numbers in sequelae groups for spina bifida or encephalocoele by GBD region, 2005 (source: Modell, 2010)

GBD Region	Total if surv = pop norm*	Total dead	Total living	Total sequ gp 1	Total sequ gp 2	Total sequ gp 3	Total sequ gp 4
Sub-Saharan Africa, Central	55,893	54,524	1,369	507	192	260	411
Sub-Saharan Africa, East	216,212	201,061	15,151	5,606	2,121	2,879	4,545
Sub-Saharan Africa, South	48,320	43,010	5,310	1,965	743	1,009	1,593
Sub-Saharan Africa, West	239,848	228,617	11,231	4,155	1,572	2,134	3,369
Middle East	324,269	263,497	60,772	22,486	8,508	11,547	18,232
North Africa	173,478	154,248	19,230	7,115	2,692	3,654	5,769
Caribbean	21,408	18,731	2,677	991	375	509	803
Latin America, Andean	34,602	28,405	6,197	2,293	868	1,177	1,859
Latin America, Central	153,284	126,539	26,745	9,895	3,744	5,081	8,023
Latin America, Southern	27,776	22,308	5,468	2,023	766	1,039	1,641
Latin America, Tropical	158,660	131,780	26,880	9,946	3,763	5,107	8,064
North America, High Income	96,193	59,679	36,514	13,510	5,112	6,938	10,954
Asia Pacific, High Income	54,628	39,035	15,593	5,769	2,183	2,963	4,678
Asia Southeast	358,187	281,224	76,963	28,476	10,775	14,623	23,089
Asia, Central Total	83,126	78,950	4,176	1,545	585	793	1,253
Asia, East	1,973,855	1,895,351	78,504	29,047	10,991	14,916	23,551
Asia, South	3,295,655	3,163,479	132,176	48,905	18,505	25,114	39,653
Europe, Central	62,316	52,553	9,763	3,612	1,367	1,855	2,929
Europe, Eastern	84,866	80,087	4,779	1,768	669	908	1,434
Europe, Western	76,720	55,382	21,338	7,895	2,987	4,054	6,401
Australasia	8,806	5,798	3,008	1,113	421	572	902
Oceania	6,485	6,089	396	146	55	75	119
World	7,554,588	6,990,345	564,243	208,770	78,994	107,206	169,273

*Total if survival age is the same as for the population for the country

Figure 1: Needs assessment flowchart for Neural Tube Defects



USS: Ultra Sound Scan, MSAFP: Maternal Serum Alpha-Feto Protein, CVS: Chorionic Villus Sampling, ToP: Termination of Pregnancy