Open neural tube defects are among the most common severely disabling birth defects [1]. A general declining trend in the incidence of NTD at birth has been observed in many countries because of a primary prevention causing reduction in the total incidence and/or due to secondary prevention by screening and termination of affected pregnancies. The studies of Smithells et al. [2], confirmed by other clinical trials, showed that supplements containing folic acid, when consumed by women before conception, could reduce the rates of neural tube defects. Accordingly, professional organizations and governmental agencies promoted the use of folic acid supplements before and during pregnancy to prevent neural tube defects. In some countries like the United States and Canada, the recommendations of supplementation are integrated with a policy of folic acid food fortification [3]. In Israel, the Public Health services in the Ministry of Health issued a circular in August 2000 containing guidelines with recommendations for 0.4 mg folic acid supplement in the preconceptional period and during pregnancy [4]. The subject was also introduced by a campaign to doctors and nurses in the well-baby clinics run by the Ministry of Health and to the four health management organizations, various professional organizations, and the public via the media [5]. Although most cereals for breakfast in Israel as well as a few types of bread are fortified also with folic acid, fortified foods represent only a small part of the diet of the majority of the population [6].

Data on the total rates of NTD (including those of terminated pregnancies) in Israel have been available since 1999 when a national registry of NTD was initiated [7]. The registry therefore includes data before and after the recommendations on folic acid supplementation, allowing monitoring and evaluating the implementation and outcome of the project.

Subjects and Methods

Reporting newborns with malformations is obligatory in Israel; the registration uses the child’s ID number. In 1999 all the medical units involved in the diagnosis of NTD either during pregnancy or at birth were informed of the establishment of a national registry and were asked to participate. The major participants came from the hospitals’ ultrasound units, genetic units, triple test laboratories, and departments of pathology. In addition, data were extracted from the National Registry of Malformations for live-born as well as stillborn infants. Many of the cases were reported twice or more to the NTD registry, however the ID numbers prevented multiple entries of cases.

While the registry includes syndromic NTD the data presented
here refer only to non-syndromic NTD, and were categorized in four groups: anencephaly, spina bifida, encephalocele, and unknown. The cases were classified according to the ethnic religious affiliation of the parents. The major religious groups in the Israeli population are Jews (81%), Muslim Arabs (15%), Christian Arabs (2%), and Druze (2%) [8]. The newborn population in 1999–2000 comprised 69.1% Jews, 26% Muslim Arabs, 2.1% Christians and 2% Druze.

Because the recommendations for preconceptional supplementation with folic acid were issued in mid-2000, the first weeks of the pregnancies that ended in 1999 and 2000 preceded publication of these guidelines. The pregnancies ending in 2002–2004 were after the recommendations. The year 2001 includes pregnancies whose first weeks were both before and after the recommendations and the data for 2001 were therefore not included in the comparisons.

Fluctuations in the rates of NTD are observed in all populations, often without apparent causes. In order to minimize the fluctuation in rates observed from year to year for the analyses, the data were grouped as before the recommendation for supplementation (1999–2000) and after supplementation (2002–2004). In addition, no statistical analysis was performed and the results are presented as pointing to a trend.

Results
The total numbers of NTD were stable in 1999 and 2000 and a decline occurred from 2002 [Table 1]. The mean total number of NTD was 103 for Jews and 93 for non-Jews in 1999–2000, and declined to 81 for Jews and 74 for non-Jews in 2002–2004. During the years the rate of pregnancy terminations for neural tube defects remained in similar ranges for the various ethnic groups: significantly higher for Jews (range 69–79%) than for Arabs and Druze (range 40–56%).

From the analyses of data grouped as before the recommendation for supplementation (1999–2000) and after supplementation (2002–2004) the trend was to a reduction in NTD rates [Table 2]. The NTD rates in the period 2002–2004 declined as compared to 1999–2000 in the two religious groups: from 11.7 to 8.1 per 10,000 live births among Jews (31% decline) and from 22 to 16.7 per 10,000 live births among non-Jews (24% decline). The reduction was from 21.1 to 18 per 10,000 live births among Druze and 16 to 8.8 per 10,000 among Muslims not including the Bedouins. Almost no changes were observed among the Christians, and in the Bedouin subgroup of Muslim Arabs there was even an elevation in the rates from 25 to 28 per 10,000 live births.

The main change observed was a reduction in the rates of spina bifida [Table 3] – from 4.9 to 2.7 per 10,000 live births among Jews (44% decline) and 9.5 to 6.2 per 10,000 live births among Arabs and Druze (34.4% decline). There was almost no change in the rates of anencephaly in both groups: from 5.3 to 4.9 per 10,000 live births among Jews and 8.9 to 8.2 per 10,000 live births among Arabs and Druze.

Discussion
Open neural tube defects are among the most common severely disabling birth defects [1]. In Israel it has been demonstrated that the prevalence is particularly high among Muslim Arabs and Druze [7]. The disparities between the different religious groups probably represent a combination of genetic differences with environmental and cultural factors. The living conditions of the Bedouins in the Galilee are close to those of the other Muslims in the region but mostly different from the Bedouins in the Negev Desert. However, a similar high prevalence of NTD is observed among the Bedouins living either in the Galilee or in the Negev.

In Israel most NTD are diagnosed during pregnancy, and between 40% and 79% are terminated [Table 1]. Therefore, while in the past, Israeli surveys of the NTD prevalence were performed at birth, nowadays it is imperative that such surveys include also termination of pregnancies. A comparison of the NTD rates among Jews in 1958–1968 at birth [9] with those from 1999–2000 including termination of pregnancies revealed a 20% decline (from

Table 1. Neural tube defects per year among Jews, Arabs and Druze*

<table>
<thead>
<tr>
<th></th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jews</td>
<td>249/99</td>
<td>31/107</td>
<td>31/99</td>
<td>19/73</td>
<td>18/87</td>
<td>25/84</td>
</tr>
<tr>
<td>(76%)</td>
<td>(71%)</td>
<td>(69%)</td>
<td>(74%)</td>
<td>(79%)</td>
<td>(70%)</td>
<td></td>
</tr>
<tr>
<td>Arabs and Druze</td>
<td>47/92</td>
<td>49/94</td>
<td>58/96</td>
<td>38/80</td>
<td>34/77</td>
<td>32/71</td>
</tr>
<tr>
<td>(51%)</td>
<td>(52%)</td>
<td>(40%)</td>
<td>(53%)</td>
<td>(56%)</td>
<td>(55%)</td>
<td></td>
</tr>
</tbody>
</table>

* For each year, the numbers in the table are the number of children born with NTD (live births + stillbirths)/total numbers of NTD. Stillbirths refer to intrauterine deaths only and do not include late terminations of pregnancies.

Table 2. Rates of NTD* in the different religious groups (per 10,000 live births)

<table>
<thead>
<tr>
<th></th>
<th>Jews</th>
<th>Christians</th>
<th>Druze</th>
<th>Muslims**</th>
<th>Bedouins</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999-2000</td>
<td>11.7</td>
<td>12</td>
<td>21.1</td>
<td>16</td>
<td>25</td>
</tr>
<tr>
<td>2002-2004</td>
<td>8.1</td>
<td>11</td>
<td>18</td>
<td>8.8</td>
<td>28</td>
</tr>
</tbody>
</table>

* Including all the NTD
** Not including Bedouins

Table 3. Rates of NTD per 10,000 live-births at different time periods

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Jews</td>
<td>Anencephaly</td>
<td>8.6</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>Spina bifida</td>
<td>6</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>Total*</td>
<td>11.7</td>
<td>8.1</td>
</tr>
<tr>
<td>Arabs and Druze</td>
<td>Anencephaly</td>
<td>8.9</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>Spina bifida</td>
<td>9.5</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>Total*</td>
<td>22.0</td>
<td>16.7</td>
</tr>
</tbody>
</table>

* Including all the NTD
Neural Tube Defects in Israel

Following the recommendation a 41% reduction occurred among Jews (from 4.9 to 2.7 per 10,000 live births) and 35% among non-Jews (from 9.5 to 6.2 per 10,000 live births). Changes in the rates of anencephaly were minimal among both Jews (from 5.3 to 4.9 per 10,000 live births) and non-Jews (from 8.9 to 8.2 per 10,000 live births). One possible explanation may be the use in recent years of the nuchal translucency test for Down syndrome screening, whereby anencephaly can be diagnosed very early in pregnancy. Many of these early-affected pregnancies would otherwise have been spontaneously aborted and not diagnosed. This early ultrasonographic diagnosis led to an increase in the total numbers of anencephaly in recent years, masking in part the reduction. However, this explanation accounts for only a small portion of the difference in the decline of rates between anencephaly and spina bifida.

Another observation supporting the effect of folic acid is that the most significant decline (31%) occurred among Jews, who also had the highest consumption of folic acid (34.8%). Among Arabs and Druze there was a 24% decline in NTD and the folic acid consumption was 21.2%. As already mentioned there were no changes in the rates of NTD among the Bedouins in the Muslim group (respectively 25 and 28 per 10,000 live births). The observation that the decline in NTD rates occurred in all religious groups supports the assumption that the reduction is not an artifact such as lower reporting in recent years. The decline was noted in both registries – stillbirth and live-born, while the data for each were obtained from independent sources. In addition, a 30% decline in the number of pregnancy terminations due to NTD was observed in recent years (Central Bureau of Statistics, unpublished data).

It should be emphasized that reports of pregnancy termination including its indication is obligatory by law, however, since the data are collected anonymously they are not used in our registry. The observation of a significant decline in NTD obtained from several independent sources supports the assumption that the decline in the NTD rates is real.

In parallel to the recommendations for folic acid supplementation, several surveys were conducted on awareness, knowledge and practice of folic acid consumption in pregnant women in Israel, demonstrating significant changes in the habits of the population. In 2000, before the recommendation, only 17.6% of the women knew about the effects of folic acid, and 5.2% took it as recommended; 2 years later the numbers rose to 77.7% and 30.5% respectively [5]. The preliminary results of a similar survey in 2005 indicate a further rise in the preconceptional use of folic acid to 35%. Therefore, the observations of stable rates in the years preceding the recommendation and the progressive decline in NTD rates accompanying both the increased knowledge of women on the importance of folic acid and the increased intake suggest that a direct link exists between the two.

Another observation supporting the effect of folic acid is that the most significant decline (31%) occurred among Jews, who also had the highest consumption of folic acid (34.8%). Among Arabs and Druze there was a 24% decline in NTD and the folic acid consumption was 21.2%. As already mentioned there were no changes in the rates of NTD among the Bedouin. Since data on their folic acid consumption are insufficient it cannot be determined whether this is due to the low intake or to differences in genetic background resulting from consanguineous marriages in the community.

An intriguing observation from other studies as well is that the reduction in NTD rates is more significant for spina bifida than for anencephaly in all religious groups. In the 3 years following the recommendation a 41% reduction occurred among Jews (from 4.9 to 2.7 per 10,000 live births) and 35% among non-Jews (from 9.5 to 6.2 per 10,000 live births). Changes in the rates of anencephaly were minimal among both Jews (from 5.3 to 4.9 per 10,000 live births) and non-Jews (from 8.9 to 8.2 per 10,000 live births). One possible explanation may be the use in recent years of the nuchal translucency test for Down syndrome screening, whereby anencephaly can be diagnosed very early in pregnancy. Many of these early-affected pregnancies would otherwise have been spontaneously aborted and not diagnosed. This early ultrasonographic diagnosis led to an increase in the total numbers of anencephaly in recent years, masking in part the reduction. However, this explanation accounts for only a small portion of the difference in the decline of rates between anencephaly and spina bifida. Another possible explanation is that higher amounts of folic acid are needed to prevent the more severe defects [10].

In a recent study covering birth defect registries from various countries and including a total of more than 13 million births, there was no detectable change in NTD rates associated with recommendations to consume folic acid [15]. Either the rates were unchanged or the rate of decline was similar to that observed during the period before the recommendations. The authors attributed this to the fact that the recommendations were not effectively implemented and therefore did not induce a sustained change in behavior in a sufficiently large proportion of women to cause measurable effects. The present study confirms other observations that if the recommendations are accompanied by effective implementation leading to an increase in the intake of folic acid, the supplementation is effective in reducing the NTD rates.

However, to a certain degree, it is very difficult or even impossible to increase the rate of utilization of folic acid supplements [16]. Therefore, the next step should be mandatory food fortification, the success of which has been demonstrated in various countries [17]. The importance of food fortification in Israel has been emphasized and planned in parallel with the effort...
to increase folic acid intake [6,18]. However, several unexpected events slowed the process and general folic acid fortification has not yet been implemented.

In light of the apparent success of folic acid in reducing NTD rates in the different communities living in Israel, continuous efforts should be made to increase the percentage of women taking the supplementation and, particularly, to institute folic acid fortification.

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If a man will begin with certainties, he shall end in doubts; but if he will be content to begin with doubts, he shall end in certainties

Francis Bacon (1561-1626), British essayist, philosopher, and statesman

A third way to silence RNA

Two well-characterized RNA silencing pathways use small RNAs. Small interfering (si)RNAs act as targeting molecules in RNA interference (RNAi), and micro-(mi)RNAs are encoded in the genome as tiny non-coding RNA genes. Although distinct, these pathways share a number of components, such as the endonuclease Dicer, which produces RNAs with a characteristic length of ~22 nucleotides (nt). Vagin et al. (Science 2006;313:320) and Lau et al. (p. 363) report the initial characterization of a third putative RNA silencing pathway in animals, characterized by ~30-nt small RNAs in the germ line – so-called repeat associated (ra) siRNAs in Drosophila and Piwi-interacting (pi) RNAs in mammals. In both cases, these RNAs map specifically either to the sense or antisense strand, but rarely to both, which suggests that, in contrast to siRNAs and miRNAs, they do not arise from double-stranded precursors. The rasi- and piRNAs purify with Piwi proteins, homologs of the Ago proteins found in RNAi and miRNA pathways. Dicer enzymes do not appear to be involved in the generation of the rasiRNAs and, intriguingly, a weak slicing activity is associated with the piRNA complex.

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