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european surveillance of
congenital anomalies

**Special Report: Primary Prevention of Congenital Anomalies in
European Countries
(December 2013)**

EUROCAT Central Registry

Room 12L09

University of Ulster

Newtownabbey, Co Antrim

Northern Ireland, BT37 0QB

Tel: +44 (0)28 90366639

Fax: +44 (0)28 90368341

Email: eurocat@ulster.ac.uk

Web: www.eurocat.ulster.ac.uk

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WHO Collaborating Centre for the Surveillance of Congenital Anomalies

About the editors

Pietro Carbone - *National Center for Rare Diseases, Istituto Superiore di Sanità, Rome, Italy*

Cristina Morciano - *National Center for Rare Diseases, Istituto Superiore di Sanità, Rome, Italy*

Domenica Taruscio - *National Center for Rare Diseases, Istituto Superiore di Sanità, Rome, Italy*

Helen Dolk - *University of Ulster, Ulster, Northern Ireland, UK*

About the chapter contributing authors

Pietro Carbone - *National Center for Rare Diseases, Istituto Superiore di Sanità, Rome, Italy*

Orietta Granata - *National Center for Rare Diseases, Istituto Superiore di Sanità, Rome, Italy*

Alberto Mantovani - *Department of Food Safety and Veterinary Public Health, Istituto Superiore di Sanità, Rome, Italy*

Cristina Morciano - *National Center for Rare Diseases, Istituto Superiore di Sanità, Rome, Italy*

Domenica Taruscio - *National Center for Rare Diseases, Istituto Superiore di Sanità, Rome, Italy*

Stefania Ruggeri - *Agricultural Research Council, Research Center for Food and Nutrition (CRA-NUT), Rome, Italy*

Elisa Calzolari - *IMER Registry (Emilia Romagna Registry of Birth Defects), Ferrara, Italy*

Amanda Neville - *IMER Registry (Emilia Romagna Registry of Birth Defects), Ferrara, Italy*

Helen Dolk - *University of Ulster, Ulster, Northern Ireland, UK*

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Contributors to the surveys

Country	Name	Affiliation	Contribute
Austria	Haeusler Martin	Dept. Ob./Gyn., Medical University of Graz, Styria, Austria	1 st questionnaire 2 nd questionnaire
Belgium	Karen Colaert	Flemish Agency on care and health, Belgium	1 st questionnaire
	Lieven De Raedt	Federal Public Service Health, Food Chain Safety and Environment, Belgium	2 nd questionnaire
Croatia	Ivo Barić	Department of Pediatrics, University Hospital Center Zagreb, Croatia	1 nd questionnaire
	Ingeborg Barisic	Children's Hospital Zagreb, Medical School University of Zagreb, Croatia	1 st questionnaire 2 nd questionnaire
Czech Republic	Milan Macek	Charles University Prague -2nd School of Medicine	1 nd questionnaire
	Antonin Sipek	National Registry of Congenital Anomalies of the Czech Republic	1 st questionnaire 2 nd questionnaire
Denmark	Marianne Christiansen	Epidemiology, University of Southern Denmark, Sdr Boulevard 23A, DK-5000 Odense C, Denmark	1 st questionnaire 2 nd questionnaire
Estonia	Vallo Tillmann	University of Tartu, Estonia	1 st questionnaire 2 nd questionnaire
Finland	Annukka Ritvanen	National Institute for Health and Welfare, Finland	1 st questionnaire
France	Babak Khoshnood, <i>(with contribution of Nathalie Lelong, Florence Rouget, Karim Tararbit)</i>	Paris Registry of Congenital Malformations, INSERM U953, Paris, France	2 nd questionnaire
Germany	Annette Queißer-Wahrendorf	Birth Registry Mainz Model, University Medical Center Mainz, Germany	1 st questionnaire
	Awi Wiesel	Birth Registry Mainz Model, University Medical Center Mainz, Germany	1 st questionnaire
	Anke Rissmann	Malformation Monitoring Centre Saxony Anhalt, Germany	1 st questionnaire 2 nd questionnaire
Hungary	Judit Béres	Department of Hungarian Congenital Abnormality Registry and Surveillance (HCAR), National Institute of Health Development, Budapest, Hungary	1 st questionnaire 2 nd questionnaire
Ireland	Dr Bob Mc Donnell	Health Service Executive, Ireland	1 st questionnaire 2 nd questionnaire
Italy	Sebastiano Bianca	Genetica medica, Arnas Garibaldi, Catania, Italy	1 st questionnaire
	Elisa Calzolari <i>(with contribution of Amanda Neville)</i>	IMER Registry (Emilia Romagna Registry of Birth Defects), Ferrara, Italy	2 nd questionnaire
	Pietro Carbone <i>(with contribution of Orietta Granata)</i>	National Center for Rare Diseases, Istituto Superiore di Sanità, Rome, Italy	1 st questionnaire
	Stefania Ruggeri	Agricultural Research Council, Research Center for Food and Nutrition (CRA-NUT), Rome, Italy	1 st questionnaire

Latvia	Jana Lepiksone	The Centre for Disease Prevention and Control, National Health Service of Latvia, Latvia	1 st questionnaire 2 nd questionnaire
Lithuania	Meile Minkauskiene	Dept. Ob./Gyn. Lithuanian University of Health Sciences Hospital, Lithuania	1 st questionnaire
Malta	Miriam Gatt	Malta Congenital Anomalies Register. Dept. of Health Information and Research, Malta	1 st questionnaire 2 nd questionnaire
Netherlands	Hermien de Walle	Eurocat Northern Netherlands, University of Groningen, Netherlands	1 st questionnaire 2 nd questionnaire
	Lolkje de Jong-van den Berg	Eurocat Northern Netherlands, University of Groningen, Netherlands	1 st questionnaire
Norway	Anne Kjersti Daltveit	Department of Public Health and Primary Health Care, University of Bergen	1 st questionnaire
	Kari Klungsøyr	Medical Birth Registry of Norway, Norwegian Institute of Public Health	2 nd questionnaire
Portugal	Paula Braz	Minister of Health, Portugal	1 st questionnaire
Republic of Moldova	Vladimir Egorov	Academy of Science of Republic of Moldova. National Center of Reproductive Health and medical Genetic. Moldavian National Registry of CA. Republic of Moldova	1 st questionnaire 2 nd questionnaire
Slovenia	Ksenija Ogrizek Pelkič	Slovenian Association for Perinatal medicine,	1 st questionnaire 2 nd questionnaire
Spain	Joan-Lluís Vives Corrons	Red Cell Pathology Unit. Hospital Clinic i Provincial University of Barcelona	1 st questionnaire
	Maria Luisa Martinez-Frias <i>(with contribution of Eva Bermejo- Sánchez)</i>	ECEMC, Research Center on Congenital Anomalies (CIAC), Rare Diseases Research Institute (IIER), Instituto de Salud Carlos III; Department of Pharmacology, Faculty of Medicine, Universidad Complutense; CIBERER U724. Madrid	1 st questionnaire 2 nd questionnaire
	Larraitz Arriola	Subdireccion de Salud Publica, San Sebastian, Basque Country	1 st questionnaire
	Carmen Martos	Centro Superior de Investigación en Salud Pública, Valencia	1 st questionnaire
UK	Edmund G Jessop	National specialised commissioning team Great Britain	1 st questionnaire
	Judith Rankin	Institute of Health & Society, Newcastle University, England	1 st questionnaire 2 nd questionnaire
	Nichola McCullough	University of Ulster (EUROCAT Central Registry) Northern Ireland	2 nd questionnaire
	David Tucker	Public Health Wales	1 st questionnaire
Ukraine	Natalia Zymak-Zakutnia	OMNI-Net Ukraine Birth Defects Program, Khmelnytskyi Perinatal Center, Ukraine	1 st questionnaire 2 nd questionnaire

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Executive summary

Introduction

Congenital Anomalies (CA) are a significant public health issue. In 2010, EUROCAT (European Surveillance of Congenital Anomalies) data indicate a live birth prevalence of CA of 176.27 *(Loane M et al, 2011)*. In the same year CA accounted for 732,000 Disability Adjusted life years lost (DALYs) in Western Europe, 274,000 DALYs in Central Europe and 898,000 DALYs in Eastern Europe *(Khoshnood B et al, 2011)*.

In recent years CA have been identified as one of the major groups of rare diseases in need of cross-border research. In this framework the Public Health Programme 2008-2013 of the European Commission has funded the EUROCAT joint action (2011-2013) which has the key objectives of improving the surveillance and the identification of strategies for primary prevention of CA (<http://www.eurocat-network.eu/aboutus/jointactioneurocat>). EUROCAT JA task force encompasses 36 associate partners, nine collaborating partners and it is structured into 9 work packages (WP). The National Centre for Rare Diseases of the Istituto Superiore di Sanità coordinates WP7 “Primary Prevention of Congenital Anomalies”. The aim of the WP7 is to establish a shared primary prevention strategy for CA by developing recommendations to be incorporated in EU MS National Plans with the support of the European project for Rare Diseases National Plans Development (EUROPLAN).

WP 7 specific objectives are:

- to collect and review public health actions relevant to primary prevention with folic acid of Neural Tube Defects (NTD) in European countries
- to collect and review public health actions relevant to primary prevention of CA in European countries
- to build a consensus approach on the inclusion of targeted CA primary prevention actions within national plans.

Structure of the report

This report is organised in the following way:

- **Part 1. Survey to map existing policies to prevent CA by raising folic acid status in European countries.**
The report describes the objective, methods and results of the survey conducted to determine policies and initiatives existing to prevent NTD by raising folic acid status in European countries.

- **Part 2. Survey on public health actions in European countries for the prevention of congenital anomalies.** The report describes the objective, methods and results of the second survey conducted to determine policies and initiatives existing to prevent CA in European countries.
- **Part 3. Conclusion and recommendations.** Based on the results of the surveys conclusions are drawn by summarizing the main findings and proposing policy recommendations to be considered for the primary prevention of congenital anomalies in national plans and strategies on rare diseases.

PART 1- Survey to map existing policies to prevent CA by raising folic acid status in European countries

Cristina Morciano, Pietro Carbone, Alberto Mantovani, Stefania Ruggeri, Orietta Granata, Domenica Taruscio

Introduction

An adequate periconceptional intake of folic acid (FA) or folate by women before and during the first month of pregnancy can markedly reduce the occurrence of the neural tube defects (NTD) (*Lumley J et al, 2001; Wolff T et al, 2009; Blencowe H, 2010; Royal College of Obstetricians and Gynaecologists, 2003*). The intake of FA during preconception period can also reduce the risk of other congenital anomalies (such as congenital heart defects, urinary tract anomalies, oral facial clefts, limb defects). There is not enough evidence to determine if folic acid prevents other birth defects (*De-Regil LM et al, 2010*).

The words “folate” and “folic acid” are often used interchangeably but there are important differences between them. Folate is the naturally-occurring form of the vitamin. Green leafy vegetables and fruit, yeast and to a lesser extent legumes, liver and eggs are good sources of dietary folate. FA is the synthetic form of folate which widely used in most supplements and in fortified foods. The use of synthetic FA is considered convenient, being cost-efficient in production and more stable than natural food folate (*Veronica E et al, 2011*). Whereas some European countries have considered mandatory or voluntary food fortification with synthetic FA as a strategy to reduce the NTD, mandatory fortification has not been adopted in the European Union, also on the basis of a report by the European Food Safety Authority (EFSA, 2009): indeed, there are still uncertainties on the safety of FA intakes in different population groups, in particular regarding the promotion of subclinical cancers and other adverse health effects in the aging population (*Mason et ., 2007; Hirsch et al, 2009*).

The purpose of the first part of this report is to illustrate the methods and results of the survey which have been conducted with the aim of providing an overview of the current policies on primary prevention of NTD by folic acid (FA) supplementation and dietary intake of folate in European countries.

Methods

The survey was developed consisting of 34 items within seven topics related to:

- 1) FA supplementation policy specifically considering: a) recommendation(s) on FA supplementation in place at national level; b) what is recommended (e.g. target population, dosage of FA, wording of the recommendation); c) any governmental support and facilities about FA supplementation in place;
- 2) educational initiatives on the role of FA supplementation;
- 3) uptake of FA;
- 4) food fortification policy; 5) recommended dietary folate intake;
- 6) the existence of any coordinated programme or studies to estimate folate/FA intake from foods or blood folate level.

The survey was prepared online (in English) using Survey Monkey® platform and it consisted in a self-administered questionnaire. The survey was launched in 8/9 November 2011 and the deadline was 15 December, 2011. The questionnaire was widely disseminated, including 68 EUROCAT Member Registries and

108 EUCERD members. This strategy was adopted to ensure that at least one complete questionnaire per European country was collected. Participants were contacted by e-mail and asked to complete the on-line survey. Non responding countries received reminders via e-mail at four weeks after the initial invitation.

Clarifications of the responses were conducted through individual follow-up calls and e-mail exchanges. As a result of those clarifications and upon respondents' approval, some changes were made to the answers initially collected. A limitation of this survey is that even with direct contact by e-mail, we achieved limited or no response from some countries. In addition, some respondents did not complete the entire survey. Time was invested in cross-checking the information provided by the respondents by consulting the EUROCAT report (EUROCAT, 2009) and ESCO Report (EFSA, 2009) as well as specific website and relevant literatures. Attempts have been made to reduce any inconsistencies in the account received by triangulating data from different sources but some may remain unsolved.

Results

Thirty-four questionnaires were returned from 22 European countries (in brackets the number of respondents per country): Austria(1), Belgium-Flanders region (1), Croatia (2) Czech Republic (2), Denmark (1), Estonia (1), Finland (1) , Germany (3), Hungary (1) Ireland (1), Italy (3), Latvia (1), Lithuania, (1), Malta (1),The Netherlands (2), Norway (1), Portugal (1,) Republic of Moldova (1), Slovenia (1), Spain (4), United Kingdom (3), Ukraine (1).

Information for those countries which did not participate in the survey (France, Poland, Sweden and Switzerland) were collected from the EUROCAT report (EUROCAT, 2009) and ESCO Report (EFSA, 2009).

1. Recommendation on FA supplementation

The majority of countries, 17 out of 26, have official recommendation(s) formulated centrally by governmental bodies: Denmark, Finland, France, Hungary, Ireland, Italy, Lithuania, Netherlands, Norway, Poland, Portugal, Rep. of Moldova, Spain, Sweden, Ukraine, UK, Switzerland. Six countries (Austria, Belgium, Czech Republic, Germany, Latvia and Slovenia) have recommendation(s) produced by non governmental bodies (scientific societies, health care associations and/or other type of professional bodies).

Croatia has adopted the FA recommendation of the Centre for Disease Control (CDC) of Atlanta. Malta has a dietary recommendation which advises pregnant women and women planning pregnancy to increase intake of food rich in folate. Estonia has not issued FA recommendation.

Additional details about when recommendation was published, what type of institution/organization/association (Governmental/Non Governmental) developed it and relevant references are available in Appendix 1, Box 1. Overall 23 out of 26 European countries have issued recommendation on FA supplementation for prevention of congenital anomalies; Austria was the first country in 1988; 14 countries issued their recommendations on FA supplementation in the 1990s, followed by six countries in the 2000s.

Our survey indicates a substantial heterogeneity across 23 countries about what information is considered in the recommendation, e.g. preventable condition, target population, recommended dosage as well as the period and type of FA daily assumption. Heterogeneity is observed also in the wording of recommendation.

Thirteen out of 23 countries recommend FA supplementation only for the prevention of NTD: Denmark, Finland, France, Germany, Ireland, Latvia, Netherlands, Norway, Poland, Portugal, Spain, Sweden, UK. Eight countries recommend FA supplementation for the prevention of NTD and other CA as well (Belgium-Flanders region,

Czech Republic, Hungary, Italy, Republic of Moldova, Slovenia, Switzerland, Ukraine); the Lithuanian recommendation had no details about the preventable conditions; no information is available on this topic for Austria.

Two different target populations are reported in the recommendations: women planning a pregnancy and women of childbearing age with a remarkable variation in wording across countries. Women planning a pregnancy are for example defined as: “all women wishing to become pregnant” “when trying to conceive”, “all women contemplating pregnancy”, “after stopping birth control pills”. Women of childbearing are often defined as: “women who could become pregnant”, “if there is any possibility that you may become pregnant”, “prior to conception”, “all fertile women that plan a pregnancy or do not actively exclude the possibility” (see Box 2, Appendix 1).

The majority of the countries recommend the periconceptional FA supplementation at a daily dose of 400 mcg (17/23, 74%; Austria, Belgium-Flanders region, Czech Republic, Denmark, Finland, France, Germany, Ireland, Italy, Lithuania, Norway, Poland, Slovenia, Spain, Sweden, Switzerland and UK). Netherland recommendation suggests 500 mcg/day as standard dosage and Republic of Moldova provided information about a 2001 recommendation in which standard dosage was 800 mg/day.

Higher doses (4000 to 5000 mcg) are reserved for women with particular health conditions (epilepsy, diabetes, etc.) or to those with a previous child affected by NTD (Austria, Belgium-Flanders region, Denmark, Finland, France, Germany Italy, Netherlands, Norway, Slovenia, Spain, Sweden, Switzerland and UK). In Hungary, Latvia and Ukraine the higher dosage recommended for women at risk is 800 mcg/day. In Czech Republic, Ireland, Lithuania and Poland there is no recommendation of any higher dosage for women at risk.

Differences exist in the recommended timing of FA assumption. Some recommendations suggest to start three months before conception (Hungary, Rep of Moldova, UK and Ukraine), others two months before pregnancy (Portugal and Slovenia). However, about half of countries suggest almost one month prior to conception (10 out of 23: Czech Republic, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, Switzerland). Austria, Belgium-Flanders region , Denmark, Ireland and Poland do not specify the pre-conception months of the FA assumption.

Seventeen out of 23 countries (74%) recommend taking FA until the 12th week of gestation (Belgium-Flanders region, Czech Republic, Denmark, Finland, Germany, Ireland, Italy, Latvia, Lithuania, Norway, Republic of Moldova, Slovenia, Spain, Sweden, Switzerland, UK, Ukraine). In Austria, France and Netherland recommendations state that FA should be taken until the 8th week of pregnancy. In some cases (Hungary, Poland and Portugal) the recommendation is a generic “during pregnancy”.

There are also differences in the recommended type of supplements across countries. In France, Ireland, Italy, Lithuania, Norway, Poland, UK (7 out of 23 countries) it is recommended to take tablets that contains only FA explaining that it is the best way to be sure that you are getting enough FA to help reduce the risk of NTD. The other countries recommend FA intake without giving any information about the form of the supplements or about the opportunity to opt for multivitamin tablets containing the recommended amount of FA.

In the majority of countries recommendation for women to take synthetic FA daily is given in addition to consuming folate from a variety of food (16 out of 23 countries; Belgium-Flanders region, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Netherlands, Norway, Slovenia, Spain, Sweden, Switzerland, UK). Dietary advice in Hungary, Ireland and UK suggests to increase consumption of fortified foods as well. Austria, Lithuania, Portugal, Republic of Moldova and Ukraine do give dietary advice in their current FA recommendations.

2. Training initiatives for health professionals

According to the information provided by representatives of 26 countries no specific training initiatives on folic acid supplementation for health care professionals were implemented in Austria, Belgium-Flanders region, Czech Republic, Estonia, Finland, Germany, Hungary, Latvia, Lithuania and Poland.

Seventeen out of 26 European countries (65%) had already implemented and/or were implementing healthcare professional training initiatives on folic acid intake for CA primary prevention (Croatia, Denmark, Finland, France, Ireland, Italy, Malta, Netherlands, Norway, Portugal, Rep. of Moldova, Slovenia, Spain, Sweden, Switzerland, UK, Ukraine).

In some countries (Croatia, Finland, Malta, UK) training activities regarding the benefits of periconceptual FA are part of general professional education implemented in national curricula for general training of health professionals (general practitioners, pediatricians, obstetricians, midwives and nurses).

Over the last twenty years governmental organizations in Italy, Spain and UK funded training initiatives as a stand-alone interventions targeted to health care professionals. In some countries, governments supported the development of guidelines and manuals/guides targeted to antenatal and prenatal care providers in which the folic acid recommendation is reported and discussed:

- ❖ **Denmark**
 - *Anbefalinger for svangreomsorgen (Recommendations for antenatal care). Sundhedsstyrelsen, 2009 – last update 2013 ([link](#))*
- ❖ **Finland**
 - *Äitiysneuvolaopas - Suosituksia äitiysneuvolatoimintaan (.Terveiden ja hyvinvoinnin laitos (THL), 2013 ([link](#))*
- ❖ **Ireland**
 - *Best Practice for Infant Feeding in Ireland: From Pre-conception Through the First Year of an Infant's Life A practical guide for healthcare professionals based on the Scientific Recommendations for a National Infant Feeding Policy, 2 nd Edition 2011. Food Safety Authority of Ireland (FSAI), 2012 ([link](#))*
 - *Nutrition for Pregnancy - Clinical Practice Guideline. Institute of Obstetricians and Gynaecologists, Royal College of Physicians of Ireland and Directorate of Clinical Strategy and Programmes, Health Service Executive (2013) ([link](#))*
- ❖ **Italy**
 - *Linea guida Gravidanza fisiologica (Guideline for Antenatal Care). Sistema Nazionale Linee Guida-Istituto Superiore di Sanità, 2010 – last update 2011 ([Link](#))*
 - *Raccomandazioni per il counseling preconcezionale (Recommendations for preconception counseling). Progetto "Pensiamoci Prima". ICBD. Alessandra Lisi International Centre, 2011. ([link](#))*
- ❖ **Netherland**
 - *Preconception care: a good beginning. Health Council of the Netherlands, 2007 ([Link](#))*
- ❖ **Norway**
 - *A National Clinical Guideline for Antenatal Care. Directorate for Health and Social Affairs, 2005 ([Link](#))*
- ❖ **Rep of Moldova**
 - *Ghid A Național de Perinatologie (National Guide on Perinatology). Chișinău, 2006 ([Link](#))*
- ❖ **Spain**
 - *Guía para la prevención de defectos congénitos (Guide for prevention of birth defects). Ministerio de Sanidad y Consumo, 2006 ([Link](#))*

❖ **Switzerland**

- L'acido folico è indispensabile per il normale sviluppo embrionale del bambino (Folic acid is essential for normal fetal growth and development of the child). Berna: Ufficio federale della sanità pubblica (UFSP), 2008 ([Link](#))

❖ **UK**

- Antenatal care - NICE clinical guideline. National Institute for Health and Clinical Excellence (NICE), 2008 - last update 2010 ([Link](#))

Other initiatives were organized and funded by private subjects such as patient advocacy groups, pharmaceutical industries in Portugal, France, Slovenia, Spain and Ukraine.

Other types of educational initiatives have been implemented in Norway and Italy. The Norwegian Agency for Health and Social Welfare has distributed a guide to health professional to inform women about folic acid and pregnancy at the time of: i) giving guidance on contraceptive devices, ii) doing pregnancy tests, iii) removing an intrauterine device, iv) selling of pregnancy tests or contraceptive devices.

A similar informative approach was reported by Italian respondents. The Italian Ministry of Health sent an official Circular/Communication in 2011 to all Regional Health Authorities (Assessorati Regionali alla Sanità) of the Italian National Health Service as well as scientific societies:

- http://www.iss.it/binary/acid2/cont/Circolare_gennaio_2011.pdf;

- http://www.iss.it/binary/acid2/cont/Circolare_marzo_2011_Integrazione.pdf).

The Italian National Centre for Rare Diseases (CNMR) of Istituto Superiore di Sanità has organised in 2009, in collaboration with the Distance Learning working group of the External Relation Office, a 5 modules training course (the 1st module on FA supplementation) on "The prevention of congenital defects in the periconceptional and peri-natal: risk factors and protective factors for pregnancy". This activity was supported by a specific project funded by the Italian Ministry of Health (*Taruscio et al, 2014*).

3. Educational initiatives for the public

Twenty one European countries (21/26; 81% of the countries; Belgium-Flanders region, Croatia, Czech Republic, Denmark, Estonia, France, Germany, Ireland, Italy, Lithuania, Malta, Netherlands, Norway, Poland, Portugal, Rep. of Moldova, Slovenia, Spain, Sweden, Switzerland, UK, Ukraine) had already implemented and/or were implementing health promotion interventions to inform public and/or women of childbearing age about the role of FA in reducing the risk for NTD. However only in a few countries (Czech Republic, Denmark, Germany, Ireland, Italy, Netherland, Norway, Spain, Sweden and UK) initiatives were developed and supported at a national level for FA promotion but they were not carried out on regular basis. At the time of our survey the Republic of Moldova had already approved and in preparation some health promotion initiatives to support periconceptional FA use. Other programmes have been implemented by both non-profit and commercial organizations but without any central coordination.

Dissemination of educational written materials (posters, leaflets, booklets etc) is a frequent strategy in place in many countries (Belgium-Flanders region, Czech Republic, Denmark, Estonia, France, Germany, Ireland, Italy, Malta, Netherland, Norway, Slovenia, Spain, Switzerland, UK).

Educational material has been distributed mainly via health care professionals waiting-rooms (general practitioners, gynaecologists, paediatricians, etc.) or during special health events. Less often the promotional documents were offered in pharmacies, drugstore, supermarket or shopping malls.

Websites have been developed to increase knowledge and use of FA (in Belgium-Flanders region, Croatia, Czech Republic, Denmark, France, Germany, Italy, Netherland, Poland, Portugal, Slovenia, Spain, Sweden, Switzerland, UK). In Italy and the Czech Republic educational initiatives targeted to school students (adolescents) were performed.

Innovative initiatives were carried out in Netherland and Sweden. In Netherland several pharmacies add a sticker on contraceptive package stating: 'If you stop using the pill because you want to become pregnant please ask your pharmacist about the use of FA before becoming pregnant'. The board of the Swedish National Food Administration annually sent a letter to women (in the 18-45 age range) in order to inform about the role of FA in spina bifida prevention alongside the distribution of free FA tablets.

According to the information provided by countries representatives no specific health education initiatives on folic acid supplementation were implemented in Austria, Finland, Hungary, Latvia and Malta.

4. Folic acid uptake

The survey also include questions about the uptake of FA. We asked respondents to provide evidence on the use of FA in the advised period. Only few countries provided updated evidence with respect to those included in EUROCAT report of 2009. Towards the end of the report development process other references were included if they were considered relevant. Data on FA use in the remaining countries are from the EUROCAT 2009 report and are available in table 1.

In Belgium a survey conducted in 2006 (n=195) estimated that 24% of women used FA before and during pregnancy and 48% during pregnancy (personal communication from Vera Nelen - Antwerpen Registry of Congenital Anomalies). Findings from a more recent survey revealed that 86,4% of women took FA during pregnancy but only 36,3% took it correctly (7,2% stopped intake too early, 40,8% started too late) (*Griens H., et al 2010*).

In Ireland the periconceptional FA uptake rose significantly from 6% (n=300) in 1996 (*Eurocat, 2009*) to 36% (n=300) in 2009 (*Delany C et al, 2011*). Finding from a national study reported that 64% of the mothers (6,936 /10,891) had taken FA before conception and 93% (10,157/10,891) had taken FA within the first trimester of pregnancy (*McNally S et al, 2012*).

In Italy the percentage of women who use FA supplementation periconceptionally increased from 6% (n=1066) in 2002 (*Pierini A et al, 2010*) to 22,1% (n=526) in years 2010 (*Lauria L et al 2011*).

Approximately over the same years the use of FA supplements in Spain rose from 8.5%-10,62% (n=1.046; n=292) in years 2001-2002 respectively (*Martinez-Frias ML et al 2003*) to 17.37% in years 2003-2004 (N=16 761) (*Martinez-Frias ML et al 2007*). A study published in 2010 documented a percentage of 19.2%, 30.2% and 66.2% (n= 782) in preconception, first month and second month of pregnancy respectively (*Navarrete-Muñoz EM et al, 2010*).

Surveys carried out in the northern part of the Netherlands (1995-2005) showed an increased use of folic acid in the advised period. The most recent figures (2005) revealed that 80% of pregnant women (n=448) used folic acid "at some time during pregnancy", while 51% during the entire advised period (*de Walle HE et al, 2008*).

In Norway supplementation with folic acid before conception or early in pregnancy was reported by 46% of women in 2000 (*Daltveit AK et al, 2004*). The Norwegian Mother and Child Cohort Study which had recruited pregnant women between 1999 and December 2008 (n=41 900) indicates a maternal self-reported use of **FA** supplements of 69% from 4 weeks before to 8 weeks after conception and 32,4% in pre-conceptual period (*Roth C et al, 2011*).

A systematic review conducted in UK have found 14 studies (survey, cohort studies, market research) carried out from the 1998 to 2003 and monitoring the use of FA (*Stockley L et al, Lund V. 2008*). These studies estimated that periconceptual folic acid use ranged from 21% to 48%. In a more recent study conducted in UK on women attending antenatal clinics (n=386), it was reported that 89 % of women consumed supplements but only 31% took FA prior to conceiving (*Lane, 2011*).

In Republic of Moldova data from the bulletin of the Ministry of Health 70% of women used FA during first trimester of gestation (*Republic of Moldova Ministry of Health, 2008*).

A cross-sectional population based study conducted in **France** revealed that the percentage of women using preconceptional FA was 15% with variation across regions (*Tort J et al, 2013*).

Table 1. Folic acid use reported in EUROCAT report 2009 for the countries in which there are not updated data.		
Country	Year of study	% Women Using Folic Acid
Austria	1998	24% some part of advised period 10% for entire advised period
Croatia	2003	69% some part of advised period 20% for entire advised period
Denmark	2000-2	22% of women who planned pregnancies took supplements at correct time
Finland	2000	19% took FA before or in early pregnancy
Germany	2000	4.3% for entire advised period
Hungary	2006	69% of pregnant women
Malta	2000	74% some part of advised period 15% for entire advised period
Poland	2005	70% some part of advised period 11% for entire advised period
Portugal	2005	24% for entire advised period
Slovenia	2007	88% some part of advised period 31% for entire advised period
Sweden	1997	8% some part of advised period
Switzerland	2003	98% some part of advised period 37% for entire advised period

[5. Governmental support and facilitation regarding FA supplementation](#)

The survey also included questions related to policies to facilitate access to FA supplementation. Ten out of 26 countries (Croatia, Finland, France, Ireland, Italy, Malta, Moldova Rep, Spain, Sweden and UK) have implemented a national policy to provide full or partial reimbursement of FA supplementation.

According to the information collected through the WP7 survey and Eurocat Report, FA supplements are 100% reimbursed by the public health systems in Croatia, Ireland, Italy, Malta, Republic of Moldova, Sweden and UK. Finland, French and Spain public health systems refund part of the cost for FA tablets. In all other European countries FA supplements are not free of charge.

It is not always clear whether these reimbursements refer only to standard dosage supplements (from 0.4 to 0.5 mg) to healthy women or also to higher dosage supplements (4-5 mg) to women considered at risk (e.g. in Malta, FA is not routinely offered to healthy women and it is given to women free of charge only in certain circumstances, as in women with epilepsy).

Additional details of it are available in Appendix 1, Box 3.

6. Fortification policies

6.1. Background: mandatory and voluntary fortification

The World Health Organization (WHO) and the Food and Agricultural Organization (FAO) refers to food fortification as: "The practice of deliberately increasing the content of an essential micronutrient, i.e. vitamins and minerals (including trace elements) in a food irrespective of whether the nutrients were originally in the food before processing or not, so as to improve the nutritional quality of the food supply and to provide a public health benefit with minimal risk to health" (*WHO/FAO, 2006*).

Within the legal framework, food fortification can be categorized as either mandatory or voluntary.

Mandatory fortification occurs when governments legally oblige food producers to fortify particular foods or categories of foods with specified micronutrients to increase their intakes at the population level. Voluntary fortification allows industry to freely add micronutrients (vitamins and/or minerals) to foods to replace of nutrients lost during processing, or to produce a substitute product with similar nutritive value or simply to enhance a product nutritional value, from marketing strategies.

In Europe, fortification is controlled by the "EC Regulation on the Addition of Vitamins, Minerals and Certain other Substances to Foods (1925/2006/EC)". This regulation sets out what nutrients are allowed to be added to food and drink, and in what forms (Additional details are available in Appendix, Box 4). In Europe there is a robust system for protecting food safety pivoting on the European Food Safety Authority (EFSA); therefore, fortification programmes at European level should be supported by the scientific advice of EFSA, including the assessment of possible health risks associated with an excess intake of a given nutrient in the general population or in some population subgroups.

Mandatory or voluntary food fortification depends on national health policies, local circumstances, and specific goals.

In December 2013, 62 countries worldwide have adopted mandatory fortification of wheat flour and maize with FA. Levels of FA fortification range from very low levels as in Kenya and in Paraguay (0.5- 0.6 ppm) up to very high levels in Ruanda and Uganda (3.2 ppm) (source: <http://www.ffinetwork.org/>). However, a comprehensive assessment of the efficacy (including the actual need for fortification) and safety of FA fortification in such different contexts appears to be still unavailable.

The effectiveness of FA mandatory fortification in the reduction of NTDs has been proven by many studies that however cover only a limited number of Countries that have adopted this policy. The available data indicate that

the effectiveness of the FA mandatory fortification is greater in areas where the baseline rate of NTDs was higher (Honein MA et al, 2001; Choumenkovitch SF et al 2002; Lopez-Camelo JS et al, 2005; De Wals P et al, 2007).

This policy led to a significant increase in daily folate intake as well as to an increase in serum folate, both increases consisting of FA, as synthetic form used in fortification distinct from food folates. A 6% reduction in congenital heart defects, much more prevalent malformations than NTDs, was also observed by Ionescu-Ittu 2009 (Ionescu-Ittu R et al, 2009).

The US scientist supporting mandatory fortification reported that no significant decrease in NTDs and other malformations occurred in Countries that adopted recommendations on pre-periconceptional FA supplementation rather than fortification (Botto LD et al., 2005; Botto LD et al, 2006). Actually, in the last decade several countries refusing fortification due to uncertainties on risk-benefit balance (see below), like the EU Member States, have put much more efforts on FA supplementation, as well as on promotion of healthy and balanced nutrition; whereas supplementation affords a highly effective prevention in women who take supplements however it is not yet available a thorough and unbiased assessment of the impact of supplementation.

Mandatory fortification has been and is the object of animated debate because FA is not devoid of potential “side effects” in the long term, calling for risk-to-benefit analysis. A upper tolerable intake level (UL) of 1 mg/day FA in the adults has been established by the Scientific Committee on Food of the European Commission (SCF, 2000) that is still unmodified; it remains to be ascertained whether fortification might lead to intakes above the UL in EU Countries with high consumption of flour-based products. Some studies raised concerns about the effects of high doses of synthetic FA, namely, an interaction with vitamin B12 in raising the risk of cognitive decline (Morris MS et al., 2007; Selhub JMM et al, 2007; Morris MS et al, 2012) and, most important, an “acceleration phenomenon” in pre-existing malignant neoplasms mainly in the colorectal tract (Kim YI, 2003; Mason JB et al., 2007; Mason JB, 2011); such studies include both experimental models and epidemiological investigations in countries, like the USA and Canada, that have adopted fortification.

The risk-benefit of FA fortification, with special attention to any possible (adverse or positive) effect on cancer incidence was discussed by EFSA (EFSA, 2009): the outcome was that, whereas the protective effects towards NTDs and other birth defects are undisputed, the data set was not sufficient to assess a dose-response relationship for the tumour-promoting effect of FA. With this uncertainty on the safety of mandatory fortification the EU took a stand in favour of the preconceptional supplementation policy. The risk-to-benefit assessment of FA mandatory fortification awaits reconsideration with the support of a more robust data set.

6.2. Mandatory fortification among European countries

At the time of our survey none of the 26 countries has implemented mandatory fortification. The Republic of Moldova (not a EU member) is the only country in Europe with specific legislation requiring the addition of iron and folic acid to wheat flour. At the time of our survey, the country’s three largest industrial mills envisaged starting fortifying in 2012, and in 2013 all bakeries would be required to use fortified flour in their products. (Number of Countries with Fortification Legislation Doubles in Eight Years – ATLANTA, 15 May 2012 - http://www.unicef.org/moldova/media_19957.html).

Before the issuing of the EFSA report (2009), two EU countries have considered FA mandatory fortification as a possible strategy to reduce the incidence of NTDs, namely UK, (Standing Advisory Committee on Nutrition, 2006) and Ireland (Food Safety Authority of Ireland, 2008).

6.3. Voluntary food fortification-among European countries

According to data of the EFSA report some countries (Belgium, Denmark, Netherland, UK) have restriction in place on the level of FA which can be added to food. In Norway and Denmark approval is required before a FA fortified food can be marketed. Breakfast cereals are most commonly FA-fortified foods across European countries. Other common fortified foods are cereal bars, biscuits, rusks, fat spreads, beverages (EFSA, 2009).

7. Recommended Dietary Intake/Allowance

Recommended Dietary Intakes/Allowance (RDA) for population use are usually compiled by Government Organism (as National Research Institutes) or nonprofit Nutrition Society. RDI indicate the levels of intake of essential nutrients on the basis of available scientific knowledge to meet nutritional needs of all healthy people they incorporate many factors to accommodate variations in absorption and metabolism.

The majority of European countries have produced their own RDA (e.g. UK Dietary Reference Values-DRV; Italian recommended daily assumption levels of nutrients - Livelli di Assunzione di Riferimento di Energia e Nutrienti per la popolazione Italiana; The Nordic Nutrition Recommendations) reporting reference intake values of nutrients for different population groups (e.g. children, adolescents, adults, pregnant women, older people).

According to data collected through the WP7 survey, RDA are available in 15 countries: Austria, Belgium - Flanders region, Croatia, Czech Republic, Finland, Germany, Hungary, Latvia, Lithuania, Ireland, Italy, Malta, Netherlands, Norway, UK.

Nine countries (Croatia, Finland, Hungary, Ireland, Italy, Latvia, Lithuania, Netherlands and UK) reported that their folate RDA consider the primary prevention of NTDs and/or other congenital anomalies.

Currently all RDA tables do not consider women planning a pregnancy as a -population subgroup for which to establish appropriate standards of nutrient intake. Nevertheless nine countries in our survey (Croatia, Czech Republic, Finland, Hungary, Ireland, Italy, Latvia, Netherlands and UK) state that women planning pregnancy are considered in their "Recommended dietary folate allowance". These responding countries could refer to the folate RDA footnotes which sometimes mention the women planning or not actively exclude a pregnancy.

Research studies and programmes are undergoing in Croatia, Finland, Hungary, Ireland, Netherlands, Republic of Moldova, Spain and UK to estimate folate status of the population.

National programmes to evaluate folate status are active in Ireland and UK.

Discussion

This mapping exercise indicates that although the preventive role of folic acid in relation to NTD was highlighted in the 1980s and subsequently reinforced by growing scientific evidence, there is still a high proportion of women in the countries surveyed who do not take taking folic acid during the recommended period.

Most countries have been undertaken a range of national and local initiatives aimed at implementing the recommendation of FA supplementation. These include national and regional campaigns and educational activities: i) to increase health professionals knowledge, ii) to increase women's awareness and uptake of FA supplementation. Written material in a plain language has been disseminated and a number of evidence based guidelines and manuals have been developed where folic acid recommendation is reported and discussed.

Nonetheless these interventions aimed at improving FA status of women planning pregnancy through changing knowledge outcomes and behavior of health professionals and women have not been delivered as part of routine care.

A recent systematic review on what types of interventions are more likely to be successful in increasing folic acid supplement uptake revealed that if the national campaigns have some success in increasing awareness and usage of FA, this effect is not sustained once the campaign has finished (*Stockley L et al, 2008*). The authors support the efficacy of training sessions, presentations in continuing medical educational courses, etc. in raising the percentage of health care professionals who recommend folic acid (*Stockley L et al, 2008*). However such initiatives have been conducted as stand-alone interventions in most of the surveyed countries.

The literature suggests a crucial component of a programme is the “time-frame sustainability, i.e. funders, policy makers, staff and community need to commit to the long –term nature of the programme: this include sustainable finances” and capacity to adapt in response to social/environmental change and to target the most disadvantaged (*Swann C et al, 2010*).

Another promising approach which requires resources is providing free of charge supplements to women of childbearing age to facilitate FA uptake (*Stockley L et al, 2008*). However only eight countries have adopted such a type of incentive with differences which may occur in coverage in different areas of the same country (e.g. UK).

Resources are required for monitoring and evaluation of initiatives (*Swann C et al, 2010*). The survey revealed that, with the exception of the Netherlands, countries have not put in place systems to monitor regularly, and evaluate and communicate periodically to stakeholders the impact of the interventions adopted.

This mapping exercise also reveals the lack of data available about FA levels used for voluntary food fortification in European countries. Studies are needed to evaluate the contribution of fortified products to folate intakes at the population levels, particularly in women of childbearing age. The potential of fortified products to lead to an excess (i.e., over the UL) FA intake in certain population groups should also be evaluated.

Recommended dietary folate intake needs to be more explicit regarding women planning pregnancy and better exploited and disseminated within Europe. This is demonstrated by some incorrect information emerging from this survey: the respondents did not report adequate/satisfactory data and bibliographic references to support their assertions. The diffusion of clear RDI information regarding women planning pregnancy for folate has to be a corner stone for efficient intervention in primary prevention.

A more coordinated and stable approach would be desirable in delivering interventions on FA supplementation and dietary folate intake allowance in EU countries, including monitoring, evaluation of uptake and communication of results to relevant stakeholders.

Further research is also needed:

- 1) to evaluate the effectiveness of interventions to promote FA supplementations and the dietary folate intake based on rigorous studies which consider the role of healthcare providers and maternal sociodemographic characteristics (i.e. Health Needs Assessment);
- 2) to evaluate further risk and benefits of mandatory folic acid fortification to the general population taking into account the complexity of the biological relation between folate and cancer, prognostic factors and longer follow-up.

PART 2 - Survey on public health actions in European countries for the prevention of congenital anomalies

Pietro Carbone, Cristina Morciano, Alberto Mantovani, Elisa Calzolari, Amanda Neville, Domenica Taruscio

Introduction

A number of risk factors have been associated with adverse pregnancy outcomes. These include maternal lifestyle (e.g. smoking, drinking alcohol, poor nutrition, use of medications), environmental risk factors (physical, chemical and biological) as well as maternal medical disorders (e.g. epilepsy, diabetes, or thyroid dysfunction) (*Flenady V et al, 2011*).

There is consensus that these risks factors are potentially modifiable, through interventions which include limiting pregnancy exposure to smoking and alcohol, screening for maternal medical disorders. Health promotion and surveillance should become part of routine health care in pre-pregnancy and the early antenatal period (*Yakoob MY et al 2009; Haws RA et al 2009; Shannon GD, 2013*).

Examples like congenital rubella syndrome, now largely controlled by vaccination programs, or the identification of teratogenic drugs, like thalidomide, reveal the importance of research and the benefits of primary prevention in this field.

The purpose of this report is to provide an overview of the current policies, recommendations and initiatives in European countries to promote preconception and antenatal care for prevention of CA other than supplementation of FA.

Methods

A questionnaire was developed to collect information about existing public health interventions (health care policies, recommendations, initiatives) related to the primary prevention of CA in European countries.

The survey consisted in a self-administered questionnaire entitled “Public health actions on primary prevention of congenital anomalies”.

Questions were related to the following topics: 1) maternal lifestyles guidelines or recommendations in place and policies or initiatives to implement them including educational initiatives; 2) policies on infectious diseases and chronic diseases; 3) policies/initiatives on drugs and medications use during pregnancy; 4) genetic counselling services; 5) policies/initiatives on controlling chemical exposure from occupational and environmental sources; 6) inclusion of primary prevention policies in the National plan for rare diseases.

Twenty seven countries were invited to participate in the survey. A unique respondent per country was involved. Two respondents were invited for UK, one for England and one for North Ireland. The questionnaire in English was submitted through Survey Monkey™ web platform on the 20th of October, 2012.

The limitations of the survey are: i) even with direct contact by e-mail we achieved limited or no response from some countries; ii) some respondents did not complete the entire survey; iii) no information was asked about the level (nationwide or regional) of the policies. Attempts have been made to reduce any inconsistencies in the account received by triangulating data from different source but some may remain.

Results

The report presents data collected from 21 out of 27 European countries: Austria, Belgium-Flanders region, Croatia, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Ireland, Italy, Latvia, Malta, Netherlands, Norway, Republic of Moldova, Slovenia, Spain, UK (England and North Ireland separately) and Ukraine.

1. Recommendations on maternal lifestyles and use of medication

Eighteen out of 21 countries have maternal lifestyle recommendations in place for primary prevention of CA. Table 2 shows which countries have issued recommendation on maternal lifestyle and use of medication.

The recommendations address both women who desire to get pregnant or are pregnant, except recommendations developed in Belgium and Czech Republic which address pregnant women only.

Among countries that issued lifestyle recommendations, alcohol consumption and smoking are the most considered health determinants (100% of countries) followed by advices on the use of medications (17 countries with exception of Ukraine), on correct hygienic behaviors (15 countries with exception of Czech Republic, Malta and Ukraine) and on the recreational/illicit drugs (14 countries with the exception of Austria, Germany, Slovenia and Ukraine).

Recommendations on maternal weight before and during pregnancy are in place only in about half of the countries. Moreover, only six countries (Denmark, France, Hungary, Netherlands, Spain, UK-England) have issued recommendations on the risk of exposures to reproductive toxicants that may be used at home or for hobbies (e.g. cleaning agents, decorating fluids, beauty products, etc.).

2. Educational initiatives to implement recommendations on maternal lifestyle and behaviour

As shown in table 2, seventeen countries reported that educational material (brochures, leaflets, websites) are available as a strategy for the implementation of recommendations on maternal lifestyle and behaviour. However only in six countries (Austria, Germany, Ireland, Italy, Spain, UK-England) the educational materials are actively distributed while in the remaining countries the provision of information is only offered when couples seek advice. Thirteen countries organise training initiatives specifically targeted to healthcare professionals involved in pre-pregnancy and pregnancy health care.

Table 2. Recommendations on maternal lifestyle and linked educational initiatives									
Countries	Recommendations on maternal lifestyle	Topic considered in the recommendations						Educational Initiatives	
		Alcohol Smoking	Medication use	Correct hygienic	Recreational/illicit drug	Maternal weight before and during pregnancy	Risk of exposures to reprotoxic agents used at home or for hobbies	Educational material	Training initiative for health professional
Austria	Yes	Yes	Yes	Yes	No	No	No	Yes	No
Belgium-Flanders region	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No
Croatia	No	---	---	---	---	---	---	---	---
Czech Republic	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes
Denmark	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Estonia	No	---	---	---	---	---	---	---	---
France	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Germany	Yes	Yes	Yes	Yes	No	No	No	Yes	No
Hungary	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ireland	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Italy,	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Latvia	No	---	---	---	---	---	---	---	---
Malta	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Netherlands	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Norway	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Rep. of Moldova	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Slovenia	Yes	Yes	Yes	Yes	No	No	No	No	No
Spain	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
UK-England	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
UK-North Ireland	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Ukraine	Yes	Yes	No	No	No	No	No	Yes	Yes

3. Infectious diseases prevention policies

Our analysis was based on the following definitions:

1. policies for evaluation of immunization status in women planning pregnancy;
2. policies for immunization of women planning pregnancy;
3. policies for evaluation of serological status during pregnancy.

The information gathered from this strand of research reveals that in the European context variation exists in the national policies in place to prevent infectious diseases associated with CA in pregnancy or in the pre-pregnancy period (see tables 3, 4, 5).

Absence of a policy may reflect in some case a considered decision. This is the case, for example, for toxoplasmosis and cytomegalovirus (CMV) in UK-England where serological testing in the antenatal care period, for healthy woman with an uncomplicated singleton pregnancy, is not recommended since is not considered cost effective (*National Institute for Health and Clinical Excellence, 2008*).

On the other hand the existence of recommendations on the offer of preconception and antenatal serological evaluation and of immunization against specific infectious diseases it does not necessarily imply that these interventions are offered free of charge to the women. Similarly, offering free of charge these interventions does not necessarily imply that they are part of a national/regional preconception and prenatal structured care programme.

It should be noted that the tables 3, 4 and 5 indicate if the preconceptional and antenatal serological evaluation for specific infectious diseases, and the preconceptional vaccination against specific infectious diseases are offered "Free Of Charge"/"Fee For Service"/"Not offered" in any circumstance (e.g. as a part of an official preconception care/vaccination programme; on demand by the woman; on recommendation of the physician/midwife/gynecologist; only for subgroup women considered at risk).

3.1 Women planning pregnancy: policies for evaluation of immunization status and for immunization

Table 3 shows which countries offer pre-conception screening free of charge for syphilis, HIV, Rubella, toxoplasmosis, HBV CMV and Varicella to women planning a pregnancy.

Pre-conception testing for syphilis and HIV are offered free of charge in 55% of the countries (11/20; of country respondents; Austria, Croatia, Czech Republic, Denmark, France, Hungary, Italy, Malta, Norway, Spain, Ukraine). Rubella testing is offered free of charge in 55% of country (11/20; Austria, Croatia, Czech Republic, Denmark, France, Italy, Malta, Norway, Spain, UK-North Ireland, Ukraine). Pre-conception testing is offered free of charge in seven countries for Toxoplasmosis (8/20; 40% of country respondents; Austria, Croatia, Czech Republic, France, Italy, Malta, Spain, Ukraine) and HBV (9/20; 45% of country respondents; Austria, Croatia, Czech Republic, Denmark, France, Hungary, Malta, Norway, Ukraine). CMV and Varicella testing are free of charge in five countries (CMV in Austria, Czech Republic, Croatia, Malta and Ukraine; Varicella in Austria, Czech Republic, Croatia, Denmark and Malta).

Most countries responded that vaccination against Rubella is offered to women planning pregnancy free of charge (15/20; 75% of country respondents; Austria, Croatia, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Italy, Malta, Norway, Republic of Moldova, Spain, UK-England, UK-North Ireland) while HBV and varicella vaccination are respectively offered free of charge in ten (10/20; 50% of country respondents; Austria, Croatia, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Malta, Spain) and six countries, (6/20; 30% of country respondents; Croatia, Czech Republic, Denmark, France, Italy, Spain). Details on the countries are available in table 4.

3.2 Pregnant women: policies for evaluation of serological status during pregnancy

Antenatal care policies are in place to evaluate free of charge the serological status of HBV, HIV and syphilis, Rubella, Toxoplasmosis in 50-60 % of the countries:

- twelve countries for Toxoplasmosis (Austria, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Ireland, Italy, Malta, UK-England; Ukraine);
- thirteen countries for Rubella (Austria, Czech Republic, Denmark, Estonia, France, Germany, Ireland, Italy, Malta, Spain, UK-England, UK-North Ireland, Ukraine);
- thirteen countries for HIV and syphilis (Czech Republic, Denmark, Estonia, France, Germany, Hungary, Italy, Malta, Republic of Moldova, Spain, UK-England, UK-North Ireland, Ukraine)

- fifteen countries for HBV (Croatia, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Ireland, Italy, Malta, Republic of Moldova, Spain, UK-England, UK-North Ireland, Ukraine);

Policies for checking serological status for CMV free of charge are much less widespread (only Czech Republic, Denmark, Estonia, Ireland, Malta, UK-England, Ukraine); varicella status is checked only in Czech Republic, Denmark, Estonia, Malta and UK-England.

Details on the countries are available in table 5.

4. Policies on maternal chronic diseases

Consensus exists on the value of implementing advice and assessment for women affected by, or identified as high-risk for, medical conditions recognized to increase the risk of CA such as diabetes or epilepsy; when effective advice is provided in the pre-pregnancy and antenatal care period, it may significantly benefit the pregnancy outcomes (*Wahabi HA et al, 2012; Walker SP et al, 2009; Prick BW et al, 2012; De Groot L et al, 2012 Murphy VE et al, 2013. Johnson K, et al, 2006*).

Table 6 shows the available information on policies for women affected by, or identified as high-risk for, medical conditions recognized to increase the risk of CA. According to the data collected a consistent preconception health care program (defined as a preconception consultation/counseling program and diagnostic testing to identify/confirm selected chronic diseases) is implemented in a minority of European countries.

Diabetes (type 1 and 2) is monitored free of charge in the framework of the preconception consultation in 8 countries (8/19; 42% of country respondents; Austria, Croatia, Czech Republic, France, Republic of Moldova, Spain, UK-England, Ukraine). Other conditions receive even less attention by preconception care programmes with differences from country to country. For example, thyroid disorders are considered in 6 out of the 19 countries; epilepsy and asthma in 5 out of the 19 countries; hyperphenylalaninemia and malabsorption disorders in 4 out of 19 countries. Countries details are available at table 6.

Antenatal “Special Care Program” for chronic diseases are defined as any program designed to help women with medically complicated pregnancies. It is an approach to health management tailored to the individual needs of pregnant women with various medical conditions or limitations meaning that they require more than routine delivery of care. They are more diffused than preconception care intervention. Diabetes (pre-gestational and gestational) is considered in 13 out of 19 countries (Austria, Croatia, Czech Republic, Denmark, France, Hungary, Italy, Malta, Norway, Spain, UK-England, UK-North Ireland, Ukraine); epilepsy in 12 out of 19 countries (Austria, Croatia, Czech Republic, Denmark, France, Hungary, Italy, Malta, Norway, Spain, UK-North Ireland, Ukraine); thyroid disorders in 11 out of 19 countries (Austria, Croatia, Czech Republic, Denmark, France, Hungary, Italy, Malta, Spain, UK-North Ireland, Ukraine).

However fewer countries include consideration of other chronic conditions in the context of routine care of pregnant women:

- hyperphenylalaninemia (8/19; 42% of respondents; Croatia, Czech Republic, Denmark, France, Hungary, Norway, UK-North Ireland, Ukraine),
- pathologies of malabsorption (6/19; 32% of respondents; Austria, Czech Republic, Denmark, France, Hungary, Norway)
- asthma (4/19; 21% of respondents; Czech Republic, France, Hungary and Malta).

Additional countries details are available at table 7.

Table 3. Are women planning pregnancy offered laboratory tests to evaluate immunization status for the following infectious diseases? (Notes: FOC= Free Of Charge; FFS= Fee For Service; NO= Not Offerd)																						
	Austria	Belgium	Croatia	Czech Republic	Denmark	Estonia	France	Germany	Hungary	Ireland	Italy	Latvia	Malta	Netherlands	Norway	Republic of Moldova	Slovenia	Spain	Switzerland	UK England	UK North Ireland	Ukraine
Toxopl.	Yes, FOC	Yes, FFS	Yes, FOC	Yes, FOC	NO	NO	Yes, FOC	Yes, FFS	Yes, FFS	NO	Yes, FOC	NO	Yes, FOC	NO	NO	Yes, FFS	---	Yes, FOC	---	NO	NO	Yes, FOC
CMV	Yes, FOC	NO	Yes, FOC	Yes, FOC	NO	NO	NO	Yes, FFS	Yes, FFS	NO	NO	NO	Yes, FOC	NO	NO	Yes, FFS	---	NO	---	NO	NO	Yes, FOC
Syphilis	Yes, FOC	NO	Yes, FOC	Yes, FOC	Yes, FOC	NO	Yes, FOC	Yes, FFS	Yes, FOC	NO	Yes, FOC	Yes, FFS	Yes, FOC	NO	Yes, FOC	Yes, FFS	---	Yes, FOC	---	NO	NO	Yes, FOC
Varicella	Yes, FOC	NO	Yes, FOC	Yes, FOC	Yes, FOC	NO	NO	NO	Yes, FFS	NO	NO	NO	Yes, FOC	NO	NO	Yes, FFS	---	NO	---	NO	NO	Yes, FFS
Rubella	Yes, FOC	Yes, FFS	Yes, FOC	Yes, FOC	Yes, FOC	NO	Yes, FOC	Yes, FFS	Yes, FFS	NO	Yes, FOC	Yes, FFS	Yes, FOC	NO	Yes, FOC	Yes, FFS	---	Yes, FOC	---	NO	Yes, FOC	Yes, FOC
HBV	Yes, FOC	NO	Yes, FOC	Yes, FOC	Yes, FOC	NO	Yes, FOC	Yes, FFS	Yes, FOC	NO	NO	Yes, FFS	Yes, FOC	NO	Yes, FOC	Yes, FFS	---	NO	---	NO	NO	Yes, FOC
HIV	Yes, FOC	NO	Yes, FOC	Yes, FOC	Yes, FOC	NO	Yes, FOC	Yes, FFS	Yes, FOC	NO	Yes, FOC	Yes, FFS	Yes, FOC	NO	Yes, FOC	Yes, FFS	---	Yes, FOC	---	NO	NO	Yes, FOC

Table 4. Are women planning pregnancy offered immunization/vaccination about the following infectious diseases?

(Notes: FOC= Free Of Charge; FFS= Fee For Service; NO= Not Offered)

	Austria	Belgium	Croatia	Czech Republic	Denmark	Estonia	France	Germany	Hungary	Ireland	Italy	Latvia	Malta	Netherlands	Norway	Republic of Moldova	Slovenia	Spain	Switzerland	UK England	UK North Ireland	Ukraine
Varicella	No	No	Yes, FOC	Yes, FOC	Yes, FOC	No	Yes, FOC	No	Yes, FFS	No	Yes, FOC	No	Yes, FFS	No	No	Yes, FFS	---	Yes, FOC	---	No	No	No
Rubella	Yes, FOC	Yes, FFS	Yes, FOC	Yes, FOC	Yes, FOC	No	Yes, FOC	No	Yes, FOC	No	Yes, FOC	Yes, FOC	---	Yes, FOC	---	Yes, FOC	Yes, FOC	No				
HBV	Yes, FOC	No	Yes, FOC	Yes, FOC	Yes, FOC	No	Yes, FOC	Yes, FOC	Yes, FOC	Yes, FOC	No	No	Yes, FOC	No	No	Yes, FFS	---	Yes, FOC	---	No	No	No

Table 5. Is the immunization status of pregnant women screened during pregnancy for the following infectious diseases?

(Notes: FOC= Free Of Charge; FFS= Fee For Service; NO= Not Offered)

	Austria	Belgium	Croatia	Czech Republic	Denmark	Estonia	France	Germany	Hungary	Ireland	Italy	Latvia	Malta	Netherlands	Norway	Republic of Moldova	Slovenia	Spain	Switzerland	UK England	UK North Ireland	Ukraine
Toxopl.	Yes, FOC	NO	---	Yes, FOC	Yes, FOC	Yes, FOC	Yes, FOC	Yes, FOC	Yes, FOC	Yes, FOC	Yes, FOC	NO	Yes, FOC	NO	NO	Yes, FFS	---	NO	---	Yes, FOC	NO	Yes, FOC
CMV	NO	NO	---	Yes, FOC	Yes, FOC	Yes, FOC	NO	NO	Yes, FFS	Yes, FOC	NO	NO	Yes, FOC	NO	NO	Yes, FFS	---	NO	---	Yes, FOC	NO	Yes, FOC
Syphils	NO	NO	---	Yes, FOC	Yes, FOC	Yes, FOC	Yes, FOC	Yes, FOC	Yes, FOC	---	Yes, FOC	NO	Yes, FOC	NO	NO	Yes, FOC	---	Yes, FOC	---	Yes, FOC	Yes, FOC	Yes, FOC
Varicella	NO	NO	---	Yes, FOC	Yes, FOC	Yes, FOC	NO	NO	Yes, FFS	NO	NO	NO	Yes, FOC	NO	NO	Yes, FFS	---	NO	---	Yes, FOC	NO	NO
Rubella	Yes, FOC	NO	---	Yes, FOC	Yes, FOC	Yes, FOC	Yes, FOC	Yes, FOC	Yes, FFS	Yes, FOC	Yes, FOC	NO	Yes, FOC	NO	NO	Yes, FFS	---	Yes, FOC	---	Yes, FOC	Yes, FOC	Yes, FOC
HBV	NO	NO	Yes, FOC	Yes, FOC	Yes, FOC	Yes, FOC	Yes, FOC	Yes, FOC	Yes, FOC	Yes, FOC	Yes, FOC	NO	Yes, FOC	NO	NO	Yes, FOC	---	Yes, FOC	---	Yes, FOC	Yes, FOC	Yes, FOC
HIV	NO	NO	---	Yes, FOC	Yes, FOC	Yes, FOC	Yes, FOC	Yes, FOC	Yes, FOC	NO	Yes, FOC	NO	Yes, FOC	NO	NO	Yes, FOC	---	Yes, FOC	---	Yes, FOC	Yes, FOC	Yes, FOC

Table 6. Is there a preconception consultation/visit program to investigate if a woman planning pregnancy has – or is at risk of developing – the following chronic diseases that might affect the pregnancy?

(Notes: FOC= Free Of Charge; FFS= Fee For Service; NO= Not Offered)

	Austria	Belgium	Croatia	Czech Republic	Denmark	Estonia ⁽¹⁾	France	Germany	Hungary	Ireland	Italy	Latvia	Malta	Netherlands	Norway	Republic of Moldova	Slovenia	Spain	Switzerland	UK England	UK North Ireland	Ukraine
Epilepsy Seizures	NO	NO	Yes, FOC	Yes, FOC	NO	---	Yes, FOC	NO	NO	NO	NO	NO	NO	NO	NO	NO	---	Yes, FOC	---	NO	NO	Yes, FOC
Diabetes mellitus	Yes, FOC	NO	Yes, FOC	Yes, FOC	NO	---	Yes, FOC	NO	NO	NO	NO	NO	NO	NO	NO	Yes, FOC	---	Yes, FOC	---	Yes, FOC	NO	Yes, FOC
Thyroid disorders	Yes, FOC	NO	Yes, FOC	Yes, FOC	NO	---	Yes, FOC	NO	NO	NO	NO	NO	NO	NO	NO	NO	---	Yes, FOC	---	NO	NO	Yes, FOC
HPA	NO	NO	Yes, FOC	Yes, FOC	NO	---	Yes, FOC	NO	NO	NO	NO	NO	NO	NO	NO	NO	---	NO	---	NO	NO	Yes, FOC
Pathol. of malabsorption	Yes, FOC	NO	NO	Yes, FOC	NO	---	Yes, FOC	NO	NO	NO	NO	NO	NO	NO	NO	NO	---	NO	---	NO	NO	Yes, FOC
Asthma	Yes, FOC	NO	NO	Yes, FOC	NO	---	Yes, FOC	NO	NO	NO	NO	NO	NO	NO	NO	NO	---	Yes, FOC	---	NO	NO	Yes, FOC

(1) Estonia dropped out the survey at this point of questionnaire.

Table 7. Is there a PRENATAL SPECIAL CARE PROGRAM for pregnant women suffering from the following diseases illness?

(Notes: FOC= Free Of Charge; FFS= Fee For Service; NO= Not Offered)

	Austria	Belgium	Croatia	Czech Republic	Denmark	Estonia	France	Germany	Hungary	Ireland	Italy	Latvia	Malta ⁽¹⁾	Netherlands	Norway	Republic of Moldova	Slovenia	Spain	Switzerland	UK England	UK North Ireland	Ukraine
Epilepsy Seizures	Yes, FOC	NO	Yes, FOC	Yes, FOC	Yes, FOC	---	Yes, FOC	NO	Yes, FOC	NO	Yes, FOC	NO	Yes, FOC	NO	Yes, FOC	NO	---	Yes, FOC	---	NO	Yes, FOC	Yes, FOC
Diabetes mellitus	Yes, FOC	NO	Yes, FOC	Yes, FOC	Yes, FOC	---	Yes, FOC	NO	Yes, FOC	NO	Yes, FOC	NO	Yes, FOC	NO	Yes, FOC	NO	---	Yes, FOC	---	Yes, FOC	Yes, FOC	Yes, FOC
Thyroid disorders	Yes, FOC	NO	Yes, FOC	Yes, FOC	Yes, FOC	---	Yes, FOC	NO	Yes, FOC	NO	Yes, FOC	NO	Yes, FOC	NO	NO	NO	---	Yes, FOC	---	NO	Yes, FOC	Yes, FOC
HPA	NO	NO	Yes, FOC	Yes, FOC	Yes, FOC	---	Yes, FOC	NO	Yes, FOC	NO	NO	NO	NO	NO	Yes, FOC	NO	---	NO	---	NO	Yes, FOC	Yes, FOC
Pathol. of malabsorption	Yes, FOC	NO	NO	Yes, FOC	Yes, FOC	---	Yes, FOC	NO	Yes, FOC	NO	NO	NO	NO	NO	Yes, FOC	NO	---	NO	---	NO	NO	NO
Asthma	NO	NO	NO	Yes, FOC	NO	---	Yes, FOC	NO	Yes, FOC	NO	NO	NO	Yes, FOC	NO	NO	NO	---	NO	---	NO	NO	NO

(1) Malta Services offered FOC through the respective clinics, not as organised prenatal "Special Care Program"

5. Educational initiatives in the field of infectious and chronic diseases

In the field of the infectious and/or chronic diseases, educational materials (brochures, leaflets, websites) were developed in 15 out of 19 countries: in seven countries (Croatia, Denmark, Ireland, Italy, Malta, Netherlands, Spain) these informative materials are passively available; eight countries (Belgium-Flanders region, France, Germany, Hungary, Norway, Republic of Moldova, UK-North Ireland, Ukraine) ensured an active distribution of these materials.

There are training initiatives targeted to health professionals for these topics in 13 out of 19 countries (68% of respondents; Belgium-Flanders region, Croatia, Denmark, France, Germany, Hungary, Italy, Latvia, Malta, Norway, Republic of Moldova, UK-North Ireland, Ukraine). Some countries have specified that training on these issues is an integral part of degree courses in midwifery and medicine as well as in the post graduate specialisation courses for medical doctors (Croatia, Denmark, Italy, Latvia, Malta, UK-North Ireland). In Norway there are courses arranged by the Norwegian Medical Association during the post graduate specialisation for obstetrics and general practice, e.g. "Evidence based antenatal care; a practical review".

6. Teratology Information Service and surveillance systems on drugs and medication use in pregnancy.

The primary task of a Teratology Information Service (TIS) is to provide healthcare professionals, and pregnant women with pertinent information on safety and risks of drugs in pregnancy (*Schaefer C, 2011*). Therefore TIS play a crucial role in preventing congenital anomalies.

Eleven out of 19 countries affirmed to have a TIS in our survey (Austria, Croatia, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Spain, UK-England, UK-North Ireland): some of them are members of European Network of Teratology Information Services (ENTIS) (*Hancock RL et al 2007*). The aim of ENTIS is to coordinate the activities of the different Teratology Information Services (TIS), and to collect and evaluate data in order to contribute to the primary prevention of birth defects and developmental disorders.

The European Union countries who participate at this network are the followings (from ENTIS website - <http://www.entis-org.eu/> Accessed on 19/05/2014)

- Austria - [Graz](#), [Vienna](#)
- Croatia - [Zagreb](#)
- Czech Republic - [Prague](#)
- Finland - [Helsinki](#)
- France - [Paris](#), [Lyon](#)
- Germany - [Berlin](#), [Ravensburg](#)
- Greece - [Athens](#), [Thessaloniki](#)
- Italy - [Bergamo](#), [Firenze](#), [Milano](#), [Padova](#), [Rome](#)
- Netherlands - ['s-Hertogenbosch](#)
- Spain - [Madrid](#), [Barcelona](#)
- Switzerland - [Lausanne](#)
- United Kingdom - [Newcastle upon Tyne](#)

Although there are not TIS in Belgium and Norway, in these countries services are available that provide support and information for healthcare professionals and population on the toxicity and risk of drugs and medication.

The Belgian Centre for Pharmacotherapeutical Information has an extensive website (<http://www.bcfi.be>) which also contains a specific chapter on pharmaceuticals for pregnancy and breast feeding (<http://www.bcfi.be/GGR/MPG/IntroN.cfm#Inl64>). This information is publicly available on the internet. Besides, every physician receives a newsletter from the Belgian Centre for Pharmacotherapeutical Information which also contains information on pharmaceuticals related to pregnancy.

In Norway there is a website (www.relis.no) and telephone service for general information about drugs and medication, where health personnel can write in / call in their questions, including questions about any possible teratogenic effects of drugs.

Only few countries (Germany, Spain and Ireland) have a national surveillance system on medication use in pregnancy. The Irish Medicine's Board (www.imb.ie) monitors the safety of medicines in Ireland including use and adverse effects of medication in pregnancy. In Spain a systematic monitoring of the medication use in pregnancy is performed by ECEMC (Spanish Collaborative Study of Congenital Malformations); however ECEMC only covers about 20% of births in the country and data are obtained only for cases with congenital anomalies and one paired-control per case.

7. Genetic counselling services

Genetic counselling (GC) services are specialised medical genetic centres, often based upon the Regional/national Health Authority boundaries. The function, elements and organisation of medical genetic services have been the subject of reports and peer reviews articles (*WHO, 2006; WHO, 2011; Battista et al 2012*), all of which support the network of specialist centres and the need for close functional interaction between centres and between elements of the service within an individual centre. There is also agreement on the need for close links between medical genetic services and other clinical specialties. This definition covers all core genetic activity.

A core genetic service is defined as an integrated clinical and laboratory service, provided for those with / concerned about a disorder with a significant genetic component, and their families (this includes inherited and sporadic genetic disorders) (*Epstein CJ, 2006*). They offer accurate clinical and genetic laboratory diagnosis, risk estimation (interpretative role) and accessible information for families/other health professionals and patient support groups (written and spoken). The general approach to this definition is that the activity generated by referral of patients to a medical geneticist or of specimens to a specialised genetic centre (including metabolic biochemistry and newborn screening centres) is included within this medical genetic services definition. Even though there needs to be clarity about inclusions and exclusions in this definition, it is important that the inter-relationships of these services are always acknowledged by commissioners.

All of respondent countries have GC services:

- in 11 countries (Belgium-Flanders region, Croatia, Denmark, France, Hungary, Italy, Latvia, Netherlands, Norway, UK-England, Ukraine) they are based on a national/regional policy and supported by laws, regulations and financing for their planning and programme implementation.
- in 8 countries (Austria, Czech Republic, Germany, Ireland, Malta, Republic of Moldova, Spain, UK- North Ireland) they are not based on a national/regional policy and supported by laws, regulations and financing for their planning and programme implementation.)

In Italy GC services are established at a regional level with different policies for each region.

Austria, Belgium-Flanders region, Germany, Latvia, Malta and Spain have a direct accessing on GC services only. Access to GC is offered exclusively through structured pathways in Ireland and Republic of Moldova. Netherlands does not provide information about the means of access to GC. In the remaining countries the access to GC is offered through both, direct accessing and structured pathways.

Sometimes patients can be addressed to GC service by general practitioner or medical specialist. GC is usually being given by medical geneticists.

GC initiatives for groups at risk have been taken in ten European countries (10/19; 53% of respondents; Austria, Belgium-Flanders region, Denmark, France, Hungary, Latvia, Malta, Netherlands, Republic of Moldova, Ukraine). In Italy there are not specific GC initiatives at national and regional level, but only local initiatives exist. These initiatives address predominantly the population with high genetic risk. Only Netherlands reported as a subgroup at risk for GC the immigrant population.

From information collected it results that GC is available in most of European countries involved in the survey, but it is not clear how much this is used for the preconceptional counselling necessary for primary prevention. In the reproductive field only some respondents reported that GC is recommended for pregnant women older than 35 years and couples who had genetic and inherited diseases in family history.

Training activities for healthcare professionals (e.g. seminars, workshops, short courses, e-learning courses, summer schools, etc.) regarding GC and testing opportunity for CA prevention are available in 13 countries (13/19; 68% of respondents; Croatia, Czech Republic, Denmark, France, Hungary, Italy, Latvia, Netherlands, Norway, Republic of Moldova, Spain, UK North Ireland, Ukraine).

Educational or promotional materials (e.g. leaflet, booklet, poster, official health website, radio/television adverts, etc.) to inform women and men regarding GC are available in thirteen countries (13/19; 68% of respondents): these informative materials are passively available in Belgium-Flanders region, France, Ireland, Italy, Republic of Moldova, Spain and UK North Ireland; an actively distribution/dissemination of these materials is ensured in Austria, Czech Republic, Hungary, Netherlands, Norway and Ukraine.

8. Risks posed by environmental and occupational exposure to toxic agents

8.1 Recommendations

Official recommendations to inform women and men about CA risks posed by exposure to toxic agents are in place in 13/19 countries (68% of respondents; Belgium-Flanders region, Croatia, Denmark, France, Germany, Hungary, Italy, Netherlands, Norway, Republic of Moldova, Spain, UK North Ireland, Ukraine).

Toxic agents mainly considered in the recommendations are chemicals, pesticides, organic solvents and industrial products (85,7 % of recommendations; all respondents except: Germany and Republic of Moldova for chemicals; Denmark and Germany for pesticides, organic solvents and industrial products), followed by chemotherapeutic agents, cleaning products, metals and ionising radiations (78,6 % of recommendations ; all respondents except: Belgium-Flanders region, Denmark and Germany for chemotherapeutic agents; Germany, Republic of Moldova and Ukraine for cleaning products; Denmark, Germany and Republic of Moldova for metals; Belgium-Flanders region, Denmark and Italy for ionising radiations). In Belgium radiation and chemotherapeutic agents are areas of federal competence.

Malta has not official recommendations on environmental and occupational risk for congenital anomalies but it has legal notices saying that pregnant workers should not be exposed to physical, biological and chemical agents.

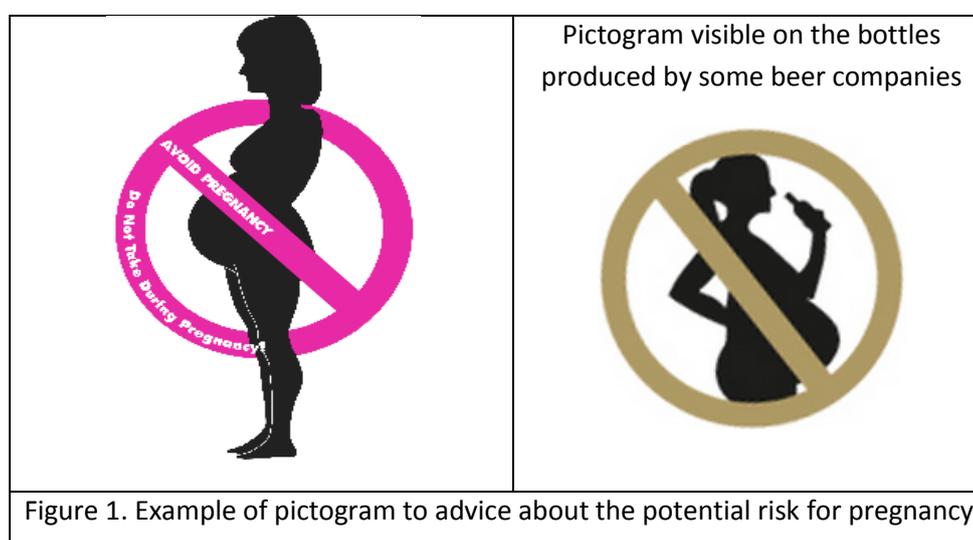
8.2. Warning labels

The United Nations Globally Harmonized System Classification and Labelling of Chemicals (GHS) “purple book” provide guidance for the classification and hazard communication for substances and mixtures and the definition of “substance” and “mixture”.

The EU Regulation 1272/2008 adopted most of GHS elements on classification, labelling and packaging of chemical substances and mixtures (Draisici R, 2011). This Regulation, also known as the ‘CLP Regulation’, gradually came to replace previous European legislation on the classification, labelling and packaging of chemicals in the EU and it is now applicative in all EU member states (Di Prospero et al, 2011). Additional details on CLP Regulation are in Appendix 1, Box 5.

Our survey indicates that there are not national requirements to have specific pictograms on consumer products (such as cosmetics, cleaning agents, paint, solvents and adhesives) to identify the reproductive risk.

Additional information other than those required by the EU regulation are rarely provided by producers and retailers of household chemical products or food/beverage. For example, at present in Europe only some alcohol producers and beer companies have chosen to voluntarily place a warning pictogram on the bottles to unambiguously inform pregnant women to totally abstain from consuming alcohol during pregnancy (The International Center for Alcohol Policies – ICAP <http://www.icap.org/table/HealthWarningLabels>) (see figure 1). Similar pictograms and/or precautionary labels (e.g. "it is safest not to use/take while pregnant" or an explicatory pictogram, Fig. 1) could be usefully extended to more consumer's products .



8.3. Urban geographic areas with high risk for environment and human health

Nine out of 19 European countries (47% of respondents; Belgium-Flanders region, Croatia, France, Hungary, Ireland, Italy, Republic of Moldova, UK, Ukraine) have identified geographic areas with high risk for environment and human health (e.g. industrial areas, waste landfills), but only in 5 countries (Croatia, France, Ireland, Italy and UK) these areas are identified by national/regional laws.

Seven countries with identified high risk areas have specific monitoring programmes for human health surveillance (Belgium-Flanders region, Croatia, France, Hungary, Italy, Republic of Moldova and Ukraine),

nevertheless only in 4 such countries CA are routinely monitored (Croatia, France, Republic of Moldova and Ukraine).

There are recommendations to reduce or eliminate health hazards/risks in high risk areas in Belgium-Flanders region, Croatia, France, Hungary, Ireland and UK. Recommendations with specific reference to reproductive and CA risks are available in Belgium-Flanders region, France and Hungary only.

8.4. Workplace

Several epidemiological studies have suggested that certain parental occupations may be associated with an increased prevalence of birth defects in offspring (Thulstrup AM et al, 2006; Desrosiers TA et al, 2012). Nearly 70% of all birth defects have no known risk factors and a large percentage of the workforce consists of women and men in reproductive age, therefore attention to the risk of birth defects due to parental occupational exposure could be of great interest. The EU has a specific directive on the protection of pregnant workers and workers who have recently given birth or are breastfeeding (Council Directive 92/85/EEC). Employers are obliged to carry out a risk assessment for these workers. They should first act to remove hazards and avoid or reduce the risks found. If it is not possible to remove the risks, the directive requires the woman to be offered alternative work, or if that is not possible, she should be suspended from work with maintenance of salary. All EU countries must ensure that the following rules are in place.

Nineteen countries have declared in our survey to have national workplace/laws or policies on hazards to reproductive health. These policies exclusively refer to women or pregnant women in 12/19 countries (63% of respondents; Austria, Belgium¹, Czech Republic, Denmark, France, Germany, Ireland, Italy, Norway, Republic of Moldova, UK-England and Ukraine). There are no gender-specific policies in the remaining seven countries (Croatia, Hungary, Latvia, Malta, Netherlands, Spain, UK-North Ireland).

According to survey, three main measures are effectively adopted in European countries for reducing the level of occupational exposures to reproductive toxicants:

- the employers should provide alternative duties for pregnant employees when there is a high risk of reproductive health effects (16/19, 84% of countries; Austria, Croatia, Czech Republic, Denmark, Germany, Hungary, Ireland, Italy, Latvia, Malta, Netherlands, Norway, Spain, UK-England, UK-North Ireland, Ukraine).
- the employers should inform women about the potential risk for pregnancy present in the workplace (14/19; 74% of countries; Croatia, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Italy, Latvia, Malta, Republic of Moldova, Spain, UK-England, UK-North Ireland).
- the employers should review their risk assessment to identify any changes that are necessary to protect the woman and the unborn baby's health (13/19; 68% of countries: Croatia, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Italy, Latvia, Malta, Netherlands, Spain, UK-North Ireland).

It is critical to note that, although these regulations are legally binding, they are oriented to an fixed employer/employee relationship and those workers on short term contracts, self employed or working without a formal contract will not be protected.

8.5. Passive smoking

There is widespread scientific consensus that exposure to passive smoking is harmful. Passive smoking is a danger to everyone, but children and pregnant women are most vulnerable (Been JV et al 2014; Pineles BL et al, 2014; Jones LL et al 2011). As a consequence smoke-free regulations in workplaces and indoor public places, (including

¹ Occupational issues are areas of federal competence in Belgium.

restaurants, bars and night clubs, as well as some open public spaces) have been introduced in a number of jurisdictions, at national or local level.

The survey shows that 13 out of 19 countries (68% of countries; Austria, Croatia, Denmark, France, Hungary, Ireland, Italy, Latvia, Malta, Norway, Spain, UK North Ireland, Ukraine) included in the current antismoking laws specific provisions for protection of pregnant women and infants by passive smoking. Many respondents were uncertain if educational initiatives are ongoing in their respective countries and it is difficult to give accurate sources and quotations.

8.6 Training activities and educational or promotional materials on environmental, home and workplace risks for CA

Training activities for healthcare professionals (e.g. seminars, workshops, short courses, e-learning courses, summer schools, etc.) regarding environmental, home and workplace risks for CA and options for prevention are available in 10 countries (10/19; 53% of countries; Croatia, France, Hungary, Italy, Netherlands, Norway, Republic of Moldova, Spain, UK North Ireland, Ukraine).

Educational or promotional materials (e.g. leaflet, booklet, poster, official health website, radio/television adverts, etc.) to inform women and men about environmental, home and workplace risks for CA are available in ten countries: these information materials are passively available in France, Ireland and Spain; an active distribution/dissemination of these materials is ensured in Denmark, Italy, Netherlands, Norway, Republic of Moldova, UK North-Ireland, Ukraine.

9. Primary prevention as part of National Plan for rare diseases

Most CA are rare (EUROCAT Working group, 2012) and the consideration of primary prevention of CA in the framework of the development and implementation of national plan and strategies for rare diseases could definitely contribute to prompt interventions and overall improvement in health.

At the time of the survey (2012), through the analysis of the responses (19 countries for these questions) to the questionnaire it was possible to identify that only three countries (Czech Republic, Denmark and Spain) have already included primary prevention of CA issues in the national plan for rare diseases, while eleven countries declared they are still working on this issue (Croatia, France, Hungary, Ireland, Italy, Latvia, Malta, Republic of Moldova, UK-England, UK-Northern Ireland, Ukraine). Five countries do not plan to include CA primary prevention in their national plan (Austria, Belgium, Germany, Netherlands, Norway,).

Discussion

This study presents an overview of the current policies and actions in place in European countries to support primary prevention interventions for CA other than periconceptional folic acid supplementation.

The majority of the countries surveyed have recommendations in place on lifestyle considerations, nonetheless strategies to implement these recommendations in the areas of behavioral modifications (for example educational and training initiative packages for women, couples and health care providers) are limited to few countries.

Though we have a reasonable repertoire of preconception evidence-based interventions for preventing infectious diseases and managing chronic diseases, it appeared that preconception care has received little policy development support in many countries.

For example, preconception vaccination and infectious diseases screening vary widely across countries. Antenatal preventive strategies seem more diffused than preconception care interventions especially in the field of chronic diseases such as diabetes, epilepsy and thyroid disorders. Other conditions, such as asthma appeared to receive less attention in the context of routine antenatal care.

Some countries have a teratology information services (TIS) in place and they are members of the European Network of Teratology Information Services. However only few countries have surveillance systems on medication use in pregnancy.

Despite progress in some countries made in the field of environmental pollution at regulatory level, our survey also highlighted the need of dedicating resources to implementing surveillance systems in areas identified at risk as well as in implementing health educational activities to minimize exposure to pollutants recognized as teratogens.

Finally, the information obtained by the key informants in each country illustrated that the implementation of policies on primary preventions of CA in several countries still rely on sporadic initiatives. The complexity of the described interventions emphasizes the importance of the development of an integrated and structured approach in delivering services. Therefore the consideration of primary prevention of CA issues in the framework of the creation an implementation of national plan of rare diseases will contribute definitely to prompt more systematic approach and political support.

PART 3 – Conclusions and policy recommendations

Domenica Taruscio, Pietro Carbone, Cristina Morciano, Helen Dolk

Many congenital anomalies (CA) are potentially preventable and liable to be reduced by an integrated strategy of primary prevention. The research presented in this report clearly outlines that in the European context there is a need for a more comprehensive, science-based and consistent approach, especially in those countries in which primary prevention actions are still in their infancy or are relying on sporadic initiatives.

Taking into account the results of the surveys as well as a review of the literature to define the main risk factors for CA, EUROCAT JA and EUROPLAN have developed the first comprehensive set of recommendations on policies to be considered for the primary prevention of CA in the European Union. These recommendations have to be considered a 'first step'. The next steps are to monitor their implementation in national plans or strategies for rare diseases, to evaluate the impact of the policy actions through continuing surveillance of CA by EUROCAT, and to regularly update the scientific evidence underpinning the recommendations.

The recommendations were developed following a consensus-based approach. Seven working groups were established composed of members of the EUROCAT JA and EUROPLAN. The working groups prepared a first draft of the recommendations (June 2012) which was reviewed several times from the standpoints of scientific soundness and national applicability. Refinements were made following the inputs from the Registry Leaders of EUROCAT network and the EUROCAT Project Management Committee.

The final document, after approval of EUROCAT Steering Committee, was sent to the policy officer at the Directorate of Public Health at the European Commission in Luxembourg (Dr. Antoni Montserrat) and was endorsed by the European Union Committee of Experts on Rare Diseases (EUCERD) in 2013 (http://www.eucerd.eu/wp-content/uploads/2013/03/Eurocat_Reco_PrimaryPrevention.pdf).

The EUCERD endorsement was an essential step, since Member State representatives of the EUCERD are involved in the elaboration of national plans or strategies for rare diseases in the respective Countries.

The final version of primary prevention recommendation, together with the other EUROPLAN recommendations, were used during EUROPLAN Meetings with policy makers (first EUROPLAN meeting was held in Rome - ISS, September 10-11, 2012); moreover, we have disseminated the recommendations among all stakeholders involved in the elaboration of national plans/strategies in Rare Diseases.

The recommendations are reported here below. They are divided in four sections: recommendations in the fields of medicinal drugs, of health services, the field of food/nutrition and lifestyle in the field of environmental pollution including the workplace.

The recommendations are recently published on "Public Health Genomics" a peer-reviewed international journal:

Taruscio D, Arriola L, Baldi F, Barisic I, Bermejo-Sánchez E, Bianchi F, Calzolari E, Carbone P, Curran R, Garne E, Gatt M, Latos-Bieleńska A, Khoshnood B, Irgens L, Mantovani A, Martínez-Frías ML, Neville A, Rißmann A, Ruggeri S, Wellesley D, Dolk H.

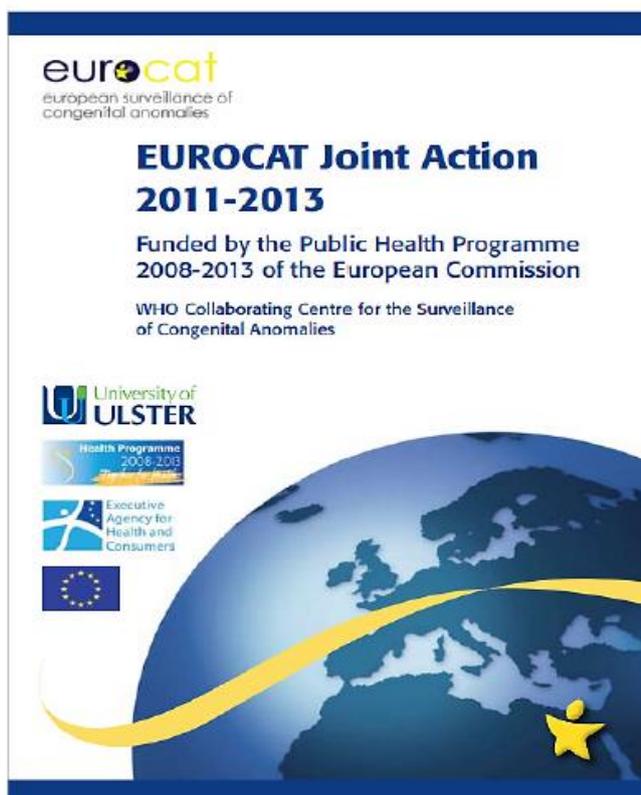
European Recommendations for Primary Prevention of Congenital Anomalies: A Joined Effort of EUROCAT and EUROPLAN Projects to Facilitate Inclusion of This Topic in the National Rare Disease Plans. Public

Health Genomics. 2014;17(2):115-23. doi: 10.1159/000360602

PRIMARY PREVENTION OF CONGENITAL ANOMALIES

EUROCAT (European Surveillance of Congenital Anomalies) and EUROPLAN (European Project for Rare Diseases National Plans Development)

Recommendations on policies to be considered for the primary prevention of congenital anomalies in National Plans and Strategies on Rare Diseases



Grant N.: 2010 22 04

www.eurocat-network.eu



Grant N.: 2011 22 01

www.europlanproject.eu

PRIMARY PREVENTION OF CONGENITAL ANOMALIES

EUROCAT (European Surveillance of Congenital Anomalies)/EUROPLAN Recommendations on policies to be considered for the primary prevention of congenital anomalies in National Plans and Strategies on Rare Diseases

Purpose of the recommendations

Most congenital anomalies are rare and form an important group of Rare Diseases, for which EU Member States are developing National Plans. Primary prevention of congenital anomalies was identified as an important action in the field of Rare Diseases in the Communication from the Commission to the European Parliament, the Council, the European economic and social committee and the committee of the regions of 11th November 2008. However, it has not been included in the Council Recommendation on an action in the field of rare diseases of 8th June 2009. This document aims at providing an outline of evidence-based policy actions for primary prevention of congenital anomalies. It does not seek to recommend specific policy options, rather to indicate the areas that Member States could target in their strategies for Primary Prevention of congenital anomalies. EUROPLAN⁽¹⁾ will support and facilitate Member States to incorporate the recommendations specified here in their National Plans, and will facilitate exchange of experience among Member States, in collaboration with EUROCAT⁽²⁾.

The causes of congenital anomalies can be environmental, genetic or an interaction involving both genes and environment⁽³⁾. Within the scope of this document, primary prevention includes any evidence-based action aimed at reducing environmental risk factors for congenital anomalies and increasing protective environmental factors. Such factors act in the periconceptual period, most often before the pregnancy has been confirmed. Whereas actions based on the precautionary principle fall mainly outside the scope of this document, in some cases precautionary actions have been quoted when they may bear significant public health and/or social benefits. Primary prevention also includes preconceptional counselling concerning genetic risk, but does not include preimplantation diagnosis.

Primary prevention of congenital anomalies includes factors that are common to other diseases as well as factors specific to congenital anomalies. Policies aimed at promoting safer foods and environment, healthy dietary habits and lifestyles as well as reducing the health impact of chronic diseases are expected to reduce the prevalence of congenital anomalies as well as many other diseases. However, elaboration of these policies needs to pay special attention to their relevance in the pre- and periconceptual period.

Rather than pinpointing specific actions, which may have a limited impact in isolation, it is advisable that Member States would integrate the different recommendations within a strategy for Primary Prevention.

The scope of policy actions needed for primary prevention of congenital anomalies

In the field of medicinal drugs

to advise women taking medication to seek medical advice before trying to get pregnant⁽⁴⁾;

to ensure that guidelines are, or are going to be, made available for physicians regarding risk-benefit balance for use of medications in pregnancy, particularly those medications used for treating chronic diseases⁽⁵⁾;

to provide a teratogen information service where specialized advice can be sought by women and professionals⁽⁶⁾;

to conduct postmarketing pharmacovigilance to detect any risk of congenital anomalies associated with use of medications, with the support of population-based congenital anomaly registries⁽⁷⁾.

In the field of food/nutrition and lifestyle

to improve folate status through periconceptional supplementation with folic acid, promotion of the consumption of foods rich in natural folates, and the appropriate use of fortified foods⁽⁸⁾

to prevent overweight/obesity and underweight⁽⁹⁻¹¹⁾;

to promote effective information on diet and nutrition in women at childbearing age, minimizing the risks of deficiency and/or overdosing of vitamins and essential trace elements⁽¹²⁾;

further to the implementation of EU food safety strategies, to prevent food contamination by recognized developmental toxicants⁽¹³⁾;

to reduce active and passive smoking⁽¹⁴⁾;

to promote alcohol avoidance in women who are pregnant or wishing to get pregnant⁽¹⁵⁻¹⁸⁾

to pay special attention to diet and lifestyles in communities with low socio-economic status or of recent immigrants.

In the field of health services

to make available preconceptional care including genetic testing and counselling for families at risk⁽¹⁹⁾;

to ensure that women with diabetes, epilepsy and other chronic diseases receive preconceptional care in order to minimize the risk of congenital anomalies⁽²⁰⁾;

to ensure evidence based vaccination policies to ensure women are protected against

infectious diseases associated with congenital anomalies and avoid contraindicated vaccinations during pregnancy⁽²¹⁾;

to include in school educational programs the awareness that congenital anomalies may be caused very early in pregnancy, often before the pregnancy is confirmed, and hence healthy practices should start preconceptionally;

to include consideration of specific pregnancy-related actions in public health action plans on all the major health determinants.

In the field of environmental pollution including the workplace

Further to the implementation of EU policies on high-concern chemicals, to ensure both regulatory actions and risk communication towards citizens in order to minimize exposure to pollutants identified as teratogens⁽²²⁾;

to ensure a suitable surveillance system where environmental risks can be identified through the integration of congenital anomaly registers with developments in biomonitoring⁽²³⁾;

to minimize exposure of pregnant workers in their workplace to risk factors for congenital anomalies (chemical, physical and biological)⁽²⁴⁾.

Types of primary preventive actions and their effectiveness

A number of types of primary preventive action can be identified:

Advice to future parents by health professionals during individual preconceptional and early pregnancy consultations, tailored for high and “low” (average population) risk couples.

Health education campaigns targeted to potential future parents.

EU-based and/or national regulatory actions which affect risk factors at source such as medicines, chemicals, infectious agents, foods, tobacco and alcohol and other recreational drugs.

Surveillance, research and evaluation generating evidence for the initiation or updating of primary preventive measures. This includes also the establishment of expert committees to review evidence.

The effectiveness of targeted actions towards primary prevention of congenital anomalies is expected to be markedly improved by:

an integrated primary prevention plan involving all relevant health professionals, thus avoiding isolated and/or uncoordinated actions/recommendations;

Implementation and refinement of EU food and environmental control programs providing

special attention to congenital anomaly risk factors;

proper evaluation and integration of new scientific knowledge into public health actions;

ensuring preconception health care in local public health programs⁽²⁵⁻²⁹⁾, while recognizing that many pregnancies are unplanned;

availability of epidemiological surveillance data from population-based congenital anomaly registers, to monitor the effectiveness of services and interventions to build a sound evidence base for policy development planning and action;

to ensure sustainability through national and international funding.

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Workpackage Leader: Domenica Taruscio.

With the contribution of: Larraitz Arriola (Basque Country-Spain), Francesca Baldi (Italy), Fabrizio Bianchi (Italy), Eva Bermejo-Sánchez (Spain), Elisa Calzolari (Italy), Pietro Carbone (Italy), Rhonda Curran (NI-UK), Helen Dolk (NI-UK), Ester Garne (Denmark), Miriam Gatt (Malta), Anna Latos-Bieleńska (Poland), Alberto Mantovani (Italy), Maria Luisa Martínez-Frías (Spain), Amanda Neville (Italy), Anke Reißmann (Germany), Stefania Ruggeri (Italy).

Amended and approved by EUROCAT Registry Leaders and members of the EUROCAT Project Management Committee June 2012 (Ingeborg Barisic, Elisa Calzolari, Rhonda Curran, Helen Dolk, Ester Garne, Lorentz Irgens, Babak Khoshnood, Domenica Taruscio, Diana Wellesley).

Project Leader of EUROCAT Joint Action: Helen Dolk.

Footnotes and Bibliography

These footnotes are intended as a brief guide to the scientific evidence and its main messages for policy, not as an exhaustive review of the evidence.

(1) European Project for Rare Diseases national Plans (EUROPLAN) - website

<http://www.europlanproject.eu>

(2) European Surveillance of Congenital Anomalies (EUROCAT) - website <http://www.eurocat-network.eu/>

(3). *In the context of these Primary Prevention recommendations, "environmental" is used in its broadest sense as non-genetic (although interacting with genetic factors), encompassing physical, chemical, biological and social factors, concentrating on factors which are potentially modifiable. This broad definition follows that of the US National Institute of Environmental Health Sciences which defines environmental exposure broadly to include not just chemical environmental pollutants, but also diet, pharmaceuticals, stress, pre-existing disease, and use of addictive substances.*

a) National Institute of Environmental Health Sciences (2012). *Advancing Science, Improving Health: A Plan for Environmental Health Research (Strategic plan 2012-2017)* (Available at: http://www.niehs.nih.gov/about/strategicplan/strategicplan2012_508.pdf)

b) National Academies Standing Committee on Use of Emerging Science for Environmental Health Decisions (2010). *The Exposome: A*

Powerful Approach for Evaluating Environmental Exposures and Their Influences on Human Disease. Newsletter 3 of the National Academies' Standing Committee on Use of Emerging Science for Environmental Health Decisions. (Available at: http://nas-sites.org/emergingscience/files/2011/05/newsletter3_exposomes-rev.pdf)

c) Seller MJ in EUROCAT (2004). EUROCAT Special Report: A Review of Environmental Risk Factors for Congenital Anomalies. pp7-29 - (Available at: <http://www.eurocat-network.eu/content/Special-Report-Env-Risk-I-and-II.pdf>).

d) Martinez-Frias, M-L (2010). Can our understanding of epigenetics assist with primary prevention of congenital defects? 47: (2). 73-80 (Available at: <http://jmg.bmj.com/content/47/2/73.full.pdf+html>)

(4) Drugs during pregnancy and lactation, Handbook of prescription drugs and comparative risk assessment. Edited by C. Schaefer. Co-authors: H. Garbis, P. McElhatton, P. Peters, M. Reuvers, E. Robert, M. Rost van Tonningen, A. Scialli. ELSEVIER, AMSTERDAM 2001.

(5) Medications of particular concern include antiepileptics, folate antimetabolites, antiblastic agents, warfarin and related anticoagulants, retinoic acid derivatives, ACE-inhibitors and AT1 receptor antagonists.

a) Henderson E, Mackillop L. (2011). Prescribing in pregnancy and during breast feeding: using principles in clinical practice. Postgrad Med J; 87(1027):349-54

However, information on the human teratogenicity of most medications is limited.

a) Rasmussen SA (2012). Human teratogens update 2011: can we ensure safety during pregnancy? Birth Defects Res A Clin Mol Teratol. 2012 Mar;94(3):123-8

b) Cassina M et al (2012). Genetic susceptibility to teratogens: State of the art. Reprod Toxicol - Epub ahead of print

There is extensive literature investigating the relative teratogenicity of different antiepileptic medication (Available at: <http://www.eurocat-network.eu/preventionandriskfactors/medicationduringpregnancy/medicationpublications>)

For antiasthmatics and antidepressants, national guidelines need to take into account the growing evidence base.

Medication During Pregnancy pages of EUROCAT

(Available at: <http://www.eurocat-network.eu/preventionandriskfactors/medicationduringpregnancy/medicationintroduction>)

(6) European Network of Teratology Information Services - website <http://www.entis-org.com/>

(7) EUROmediCAT Project - website <http://euromedicat.eu/whatiseuromedicat>

(8) Strong scientific evidence showed folate rich diet and periconceptional supplementation with folic acid (the synthetic form) is effective in reducing the prevalence of Neural Tube Defects (NTD) and other congenital malformations, and an adequate folate status in women before pregnancy is a protective factor toward these pathologies. In 2009 EUROCAT published a special report highlighting that the majority of women in Europe were still not taking folic acid preconceptionally and/or were beginning to take it too late to prevent congenital anomalies after their pregnancy had been confirmed. As a result, the impact of policy on the rate of NTD in the population was minimal, and socioeconomic inequalities widen due to differences in knowledge. Furthermore the dietary intake of folates may not be sufficient to protect vulnerable women. Many non-European countries, such as U.S.A. and Canada, have instituted mandatory food (flour) fortification with folic acid as a way forward, with a positive impact in reducing NTD prevalence. However, fortification also raises concerns about the possible "side effects" of high folic acid intake in non-target population groups, which might be related to increased cancer promotion. In 2009 the scientific committee organised by EFSA concluded "There are currently insufficient data to allow a full quantitative risk assessment of folic acid and cancer or to determine whether there is a dose-response relationship or a threshold level of folic acid intake associated with potential colorectal cancer risk. The current evidence does not show an association between high folic acid intakes and cancer risk but neither do they confidently exclude a risk. The uncertainties in relation to cancer risk highlight the importance of ensuring monitoring systems are set up for assessment of folic acid intake and status and NTD and cancer incidence in countries that decide to introduce mandatory fortification."

a) De Wals P et al (2007). Reduction in neural-tube defects after folic acid fortification in Canada. N Engl J Med. 2007; 357(2):135-42.

b) EUROCAT (2009). EUROCAT Special Report: Prevention of Neural Tube Defects by Periconceptional Folic Acid Supplementation in Europe. EUROCAT Central Registry, University of Ulster. (available at <http://www.eurocat-network.eu/content/Special-Report-NTD-3rdEd-Part-I.pdf>).

To view all EUROCAT publications on folic acid access the following link <http://www.eurocat->

c) EFSA (European Food Safety Authority), 2009. ESCO report prepared by the EFSA Scientific Cooperation Working Group on Analysis of Risks and Benefits of Fortification of Food with Folic Acid.

(Available at: <http://www.efsa.europa.eu/en/scdocs/scdoc/3e.htm>)

d) Taruscio D et al (2011). Folic acid and primary prevention of birth defects. *Biofactors*. 37(4):280-4.

(9) Stothard KJ et al (2009). Maternal overweight and obesity and the risk of congenital anomalies. A systematic review and meta-analysis. *JAMA*, 301 (6), 636-650.

(Available at: <http://jama.ama-assn.org/content/301/6/636.full.pdf+html>)

(10) Martinez-Frias ML, Frias JP, Bermejo E, Rodriguez-Pinilla E, Prieto L and Frias JL (2005). Pre-gestational maternal body mass index predicts an increased risk of congenital malformations in infants of mothers with gestational diabetes. *Diabetic Medicine*. 22: 775-781.

(11) Siega-Riz AM et al (2009). National Birth Defects Prevention Study. The joint effects of maternal prepregnancy body mass index and age on the risk of gastroschisis. *Paediatr Perinat Epidemiol*. 23(1):51-7.

(12) Particular attention should be given to:

- deficiency of Vitamin B12 and B6, since they are needed for proper metabolism of folates;
- Zinc deficiency as a risk factor for neural tube defects in communities from developing Countries.

In addition pregnant women should avoid an excessive exposure to vitamin A associated to liver consumption and taking supplements containing vitamin A.

a) Simpson JL, et al (2010). Micronutrients and women of reproductive potential: required dietary intake and consequences of dietary deficiency or excess. Part I--Folate, Vitamin B12, Vitamin B6. *J Matern Fetal Neonatal Med*. 2010 Dec; 23(12):1323-43.

b) Simpson JL, et al (2011). Micronutrients and women of reproductive potential: required dietary intake and consequences of dietary deficiency or excess. Part II--vitamin D, vitamin A, iron, zinc, iodine, essential fatty acids. *J Matern Fetal Neonatal Med*. 2011 Jan; 24(1):1-24.

c) Dey AC et al (2010). Maternal and neonatal serum zinc level and its relationship with neural tube defects. *J Health Popul Nutr*. 28(4):343-50.

d) SCF/CS/NUT/UPPLEV/24 (2002) Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Preformed Vitamin A (retinol and retinyl esters)

(Available at: http://ec.europa.eu/food/fs/sc/scf/out145_en.pdf)

e) Duerbeck NB, Dowling DD (2012). Vitamin A: too much of a good thing? *Obstet Gynecol Surv*. 67(2):122-8.

(13) A recognized example of a food contaminant highly relevant to the safety of the unborn child is methyl mercury in certain fish groups.

a) Opinion of the Scientific Panel on Contaminants in the Food Chain on a request from the Commission related to mercury and methylmercury in food (Request N° EFSA-Q-2003-030) *The EFSA Journal* (2004) 34, 1-14

b) US Food and Drug Administration:

- <http://www.fda.gov/Food/ResourcesForYou/HealthEducators/ucm081877.htm> (7/03/2012)

- <http://www.fda.gov/Food/ResourcesForYou/HealthEducators/ucm083324.htm> (7/03/2012)

The developmental hazards (especially urogenital malformations) from dietary exposure to endocrine disrupters also deserve consideration, see also below Environment.

a) Giordano F et al (2008). Maternal diet and the risk of hypospadias and cryptorchidism in the offspring. *Paediatr Perinat Epidemiol*. 2008 May;22(3):249-60

(14) Active Smoking is a risk factor for congenital anomalies.

- a) Hackshaw, A. et al. (2011). Maternal smoking in pregnancy and birth defects: a systematic review based on 173 687 malformed cases and 11.7 million controls. *Human Reproduction*, 17 (5), 589-604. (Available at: <http://humupd.oxfordjournals.org/content/17/5/589.full.pdf+html>)

The evidence regarding passive smoking is more difficult to establish, but is considered to be biologically plausible

- a) Leonardi-Bee J, Britton J, Venn A. (2011). Secondhand smoke and adverse fetal outcomes in nonsmoking pregnant women: a meta-analysis. *Pediatrics* 2011;127:734-41]

(15) Clarren SK (1981). Recognition of fetal alcohol syndrome. *JAMA*; 245:2436-9.

(16) Martinez-Frias ML, Bermejo E, Rodriguez-Pinilla E, Frias JL (2004). Risk for congenital anomalies associated with different sporadic and daily doses of alcohol consumption during pregnancy: A case-control study. *Birth Defects Research (Part A)* 70:194-200.

(17) Streissguth AP, Aase JM, Clarren SK, Randels SP, LaDue RA, Smith DF (1991). Fetal alcohol syndrome in adolescents and adults. *JAMA*; 265:1961-1967.

(18) Werler MM, Lammer EJ, Rosenberg L, Mitchell AA (1991). Maternal alcohol use in relation to selected birth defects. *Am J Epidemiol*;134:691-8.

(19) Preconception health refers to the health of women and men during their reproductive years. It focuses on steps that women, men, and health professionals can take to reduce risks, promote healthy lifestyles, and increase readiness for pregnancy.

- a) Yoon P W et al (2002). Can family history be used as a tool for public health and preventive medicine? *Genetics in Medicine*; Vol 4 no. 4 Jul/Aug 2002.
- b) Jack B W et al (2008). The clinical content of preconception care: an overview and preparation of this supplement. *Am J Obstet Gynecol*;199(6 Suppl 2):S266-79.
- c) Emery JD, Dunlop AL, Ten Kate LP. J (2012). *Community Genet.* 2012 Jun 29 - Epub ahead of print.

Proposed Recommendations from published research and recommendations from the Centers for Disease Control and Prevention (CDC):

Individual Responsibility Across the Life Span - Each woman, man, and couple should be encouraged to have a reproductive life plan. Individuals identified as having a family history of developmental delays, congenital anomalies, or other genetic disorders should be offered a referral to an appropriate specialist to better quantify the risk to a potential pregnancy.

Health Professionals responsibility - The challenge for health professionals is to reach women and men with these interventions at the time they will be most effective in reducing risks. Suspected genetic disorders might require further workup prior to conception. Known or discovered genetic conditions should be managed optimally before and after conception.

As a part of primary care visits, provide risk assessment and educational and health promotion counselling to all women of childbearing age to reduce reproductive risk and improve pregnancy outcomes.

Consumer Awareness - Increase public awareness of the importance of preconception health behaviours and preconception care services by using information and tools appropriate across various ages; literacy, including health literacy; and cultural/linguistic contexts.

Research - Increase the evidence base and promote the use of evidence to improve preconception health.

Monitoring improvements - Maximize public health surveillance and related research mechanisms to monitor preconception health.

Pearls for Practice

Women should also be informed that preconception care can improve health outcomes for both mother and baby. First, ask every woman of reproductive age whether she intends to become pregnant in the next year. Asking every woman about her reproductive intentions promotes the idea that pregnancies should be intended. Second, inform women that health conditions and medications can affect pregnancy outcomes. *J Am Board Fam Med.* 2007; 20:81-84.

During preconception screening visits, clinicians should focus on issues such as folate supplementation, hypothyroidism management, obesity control, hepatitis B vaccination for at risk women, and rubella vaccination among previously unvaccinated women.

(20) Maternal Diabetes is a well established risk factor for congenital anomalies, but the excess risk can be almost eliminated with good glycaemic control. Health services must be organized to ensure that all women with diabetes have preconceptional care to achieve

optimal glycaemic control.

- a) Garne E et al (2012). Spectrum of congenital anomalies in pregnancies with pregestational diabetes. *Birth Defects Research (Part A)*. 94: 134-140.
- b) Martinez-Frias ML et al (2005): Pre-gestational maternal body mass index predicts an increased risk of congenital malformations in infants of mothers with gestational diabetes. *Diabetic Medicine* 22:775-781

(21) Vaccination against maternal rubella is a core element of any primary preventive strategy as rubella during pregnancy is a strong teratogen. Countries should consider their coverage of women, whether immigrant women are offered vaccination, and whether women found at first pregnancy not to be immune are offered vaccinations to protect them in subsequent pregnancies. Other vaccinations should also be considered. Vaccination during the first trimester should only be given where there is evidence of safety or evidence of a favourable benefit-risk balance.

- a) Gall SA, Poland GA (2011). A maternal immunization program (MIP): developing a schedule and platform for routine immunization during pregnancy. *Vaccine*; 29(51):9411-3.

Guidelines for vaccinating pregnant women available at: http://www.cdc.gov/vaccines/pubs/downloads/b_preg_guide.pdf

(22) The “environment” as used here is all the physical, chemical and biological factors external to the human host, and all related behaviours, but excluding those natural environments that cannot reasonably be modified. This definition excludes behaviour not related to environment, as well as behaviour related to the social and cultural environment, genetics, and parts of the natural environment.

- a) Prüss-stün A, Corvalan C (2006). Preventing disease through health environments. Towards an estimate of the environmental burden of disease Geneva: World Health Organization; 2006

In the field of the environmental causes of congenital anomalies evidence is still limited and inadequate to show a causal association; however, the biological plausibility and special vulnerability of the fetus supports precautionary actions (Communication from the European Commission on the precautionary principle. Brussels - 2000). In particular, reduction of the level of exposure to hazards acting on a large-scale, such as air pollutants, byproducts of drinking water disinfection and pesticides should be recommended.

- a) Dolk H. and Vrijheid M. (2003). The impact of environmental pollution on congenital anomalies. *British Medical Bulletin*, 68, 25-45 (Available at: <http://bmb.oxfordjournals.org/content/68/1/25.full.pdf+html>).
- b) Stillerman KP et al (2008). Environmental exposures and adverse pregnancy outcomes: a review of the science. *Reprod Sci*;15(7):631-50.
- c) Vrijheid M et al (2011). Ambient Air Pollution and Risk of Congenital Anomalies: A Systematic Review and Meta-analysis. *Environ Health Perspect*; 119(5): 598-606.
- d) Shirangi A et al (2011). Living near agricultural pesticide applications and the risk of adverse reproductive outcomes: a review of the literature. *Paediatr Perinat Epidemiol*. 2011 Mar;25(2):172-91.
- e) Righi E et al (2012). Trihalomethanes, chlorite, chlorate in drinking water and risk of congenital anomalies: A population-based case-control study in Northern Italy. *Environ Res*;116:66-73.

Endocrine disrupters are recognized risk factors for reproductive disorders during puberty and adulthood; however, evidence indicates that higher exposure levels may increase the incidence of urogenital malformations such as cryptorchidism and hypospadias.

- a) Carbone P et al (2007). The possible role of endocrine disrupting chemicals in the aetiology of cryptorchidism and hypospadias: a population-based case-control study in rural Sicily. *Int J Androl*;30(1):3-13.
- b) Fernandez MF et al (2007). Human exposure to endocrine-disrupting chemicals and prenatal risk factors for cryptorchidism and hypospadias: a nested case-control study. *Environ Health Perspect*;115 Suppl 1:8-14. c) Giordano F et al (2010). Maternal exposures to endocrine disrupting chemicals and hypospadias in offspring. *Birth Defects Res A Clin Mol Teratol*;88(4):241-50; Toppari J et al (2010). Cryptorchidism and hypospadias as a sign of testicular dysgenesis syndrome (TDS): environmental connection. *Birth Defects Res A Clin Mol Teratol*;88(10):910-9.]

(23) There is a general consensus that further elucidation of the links between environmental exposures and congenital anomalies must come through linking biomarkers and congenital anomaly surveillance approaches.

- a) Schoeters GE et al. (2011). Biomonitoring and biomarkers to unravel the risks from prenatal environmental exposures for later health outcomes. *Am J Clin Nutr*. 94(suppl):1964S-9S (Available at: http://www.ajcn.org/content/94/6_Suppl/1964S.full.pdf+html)

(24) Pregnant women at work must be protected from teratogenic exposures. The challenge is to do this in early pregnancy, often before the pregnancy has been confirmed or employers are made aware. This issue should be addressed in occupational health policies. Occupational exposures of concern include pesticides, any endocrine disrupting exposure and organic solvents.

- a) Cordier S et al (1992). Maternal occupational exposure and congenital malformations. *Scandinavian Journal of Work, Environment and Health*. 18: 11-17.
- b) Cordier S et al (1997). Congenital malformations and maternal occupational exposure to glycol ethers. *Epidemiology*. 8: (4). 355-363.
- c) Figà-Talamanca I. Occupational risk factors and reproductive health of women. *Occup Med (Lond)*;56(8):521-31.
- d) Chevrier C et al (2006). Occupational exposure to organic solvent mixtures during pregnancy and the risk of non-syndromic oral clefts. *Occup Environ Med*; 63(9):617-23.
- e) Ormond G et al (2009). Endocrine disruptors in the workplace, hair spray, folate supplementation, and risk of hypospadias: case-control study. *Environ Health Perspect*;117(2):303-7
- f) Nassar N et al (2010). Parental occupational exposure to potential endocrine disrupting chemicals and risk of hypospadias in infants. *Occup Environ Med*. 2010 Sep;67(9):585-9.
- g) Vaktskjold A, Talykova LV, Nieboer E. (2011). Congenital anomalies in newborns to women employed in jobs with frequent exposure to organic solvents—a register-based prospective study. *BMC Pregnancy Childbirth*;11:83.
- h) Morales-Suárez-Varela MM et al (2011). Parental occupational exposure to endocrine disrupting chemicals and male genital malformations: a study in the Danish National Birth Cohort study. *Environ Health*;10(1):3

(25) Health Council of the Netherlands. *Preconception care: a good beginning*. The Hague: Health Council of the Netherlands, 2007; publication no. 2007/19. ISBN 978-90-5549-678-5

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(27) Frey KA, Files JA. Preconception healthcare: what women know and believe. *Matern Child Health J*. 2006 Sep;10(5 Suppl):S73-7.

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WHO/FAO (2006). *Guidelines on food fortification with micronutrients*. Geneva, Switzerland

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APPENDIX I

Box 1. Recommendations for FA supplementation in Europe			
Country	Governmental	Year	Comments and references
Austria	No	1988	<i>Pollak A, Gruber W, Birnbacher R, Zwiauer K (1998). Richtlinien zur Praevention von Neural rohre defekten durch perikonzeptionelle Folsaeure substitution (Guidelines for the prevention of neural tubes defects by periconceptual folic acid substitution). Gynaekologisch-geburtshilfliche Rundschau Vol. 38 (1) pp 55-56.</i> Austrian Pediatric Society and Austrian Society for Prenatal and Perinatal Medicine
Belgium-Flanders region	No	2009	<i>No Governmental Recommendation made in 2009 by Koninklijke Academie Voor Geneeskunde van België en Domus Medica</i> [→ http://www.health.fgov.be/internet2Prd/groups/@public/@shc/documents/ie2form/19066661.pdf] Not accessible password protected Royal Academy of Medicine of Belgium and Domus Medic
Croatia	Not applicable	Not applicable	Croatia has adopted the FA recommendation of the Centre for Disease Control (CDC) of Atlanta.
Czech Republic	No	2010	Program primární prevence - Výživa a těhotenství (Primary Prevention Program - Nutrition and pregnancy) [→ http://www.vrozene-vady.cz/primarni-prevence/index.php?co=vyziva (in Czech)] National Registry of Congenital Anomalies of the Czech Republic
Denmark	Yes	1997	Rasmussen LB, Andersen NL, Andersson G, Lange AP, Rasmussen K, Skak-Iversen L, Skovby F, Ovesen L. (1998). Folate and neural tube defects: recommendations froma Danish working group. Dan Med Bull, vol 45: 213-17 Kosttilskud. Under graviditeten er behovet for de fleste vitaminer og mineraler lidt større end normalt. (Supplements during pregnancy, the need for most vitamins and minerals slightly larger than normal) [→ http://www.altomkost.dk/Anbefalinger/Gravide/Kosttilskud/forside.htm (In Danish)] Danish Veterinary and Food Administration
Estonia	Not applicable	Not applicable	Estonia has not issued FA recommendation.
Finland	Yes	2004	Hasunen K, Kalavainen M, Keinonen H, Lagström H, Lyytikäinen A, Nurttila A, Peltola T, Talvia S (2004). The Child, Family and Food. Nutrition recommendations for infants and young children as well as pregnant and breastfeeding mothers. Helsinki 2004.

Box 1. Recommendations for FA supplementation in Europe

			Publications of the Ministry of Social Affairs and Health 2004:11 Ministry of Social Affairs and Health
France	Yes	2000	<p><i>Dehé S, Vodovar V, Vérité V, Goujard J (2000), "Prevention primaire des anomalies de fermeture du tube neural par supplementation periconceptionnelle en acide folique. Situation à Paris en 1999 (Primary prevention of neural tube defects by supplementation in folic acid. 1999 status in Paris)" BEH (Bulletin épidémiologique hebdomadaire), Vol 21, pp 87-9</i> [→http://www.invs.sante.fr/beh/2000/0021/beh_21_2000.pdf (in French)]</p> <p>Recommandation officielle de la France sur la Prévention des anomalies de fermeture du tube neural (France official recommendation on neural tube defects) [→http://www.vitamineb9.be/chargement/fr/recom_france.pdf (in French)]</p> <p>French National Authority for Health</p>
Germany	No	1995	<p><i>Koletzko B, von Kries R. (1995): Prävention von Neuralrohrdefekten durch Folsäurezufuhr in der Frühschwangerschaft (Prevention of neural tube defects by folic acid intake in early pregnancy). Gynäkologische und Geburtshilfliche Rundschau Vol 35, 2-5.</i></p> <p><i>Koletzko B, von Kries R. (1995): Prävention von Neuralrohrdefekten durch Folsäurezufuhr in der Frühschwangerschaft (Prevention of neural tube defects by folic acid intake in early pregnancy). Der Kinderarzt Vol 26, 187-190.</i></p> <p>Folsäure und Schwangerschaft (Folic acid and pregnancy) [→http://www.dge.de/modules.php?name=News&file=article&sid=318 (in German)]</p> <p>German Nutrition Society, German Society of Obstetrics and Gynaecology, German Society of Human Genetics German Society of Paediatrics and Adolescent Medicine German Society of Neuropaediatrics</p>
Hungary	Yes	1994/1996	<p><i>Szülészeti és Nőgyógyászati Szakmai Kollégium (National Board of Hungarian Gynaecologists): Szakmai állásfoglalás a terhesség alatti vitamin és ásványi anyag suplementatio kérdéséről (Guideline for vitamin and mineral supplementation during pregnancy). Magyar Nőorvosok Lapja, 62(1): 63-65, 1999. (in Hungarian)</i></p>

Box 1. Recommendations for FA supplementation in Europe

Ireland	Yes	1993	<p>http://www.folicacid.ie/ (website not available)</p> <p><i>Food Safety Authority of Ireland, Department of Health and Children (2006) Report of the National Committee on Folic Acid Food Fortification, Food Safety Authority of Ireland, Dublin</i></p> <p>[→http://www.fsai.ie/assets/0/86/204/ca0a6f81-e3a1-4e7c-8284-bc363f8ed091.pdf]</p> <p>Food Safety Authority of Ireland, Irish Department of Health and Children</p>
Italy	Yes	2004	<p>Raccomandazione per la riduzione del rischio di difetti congeniti (Recommendation for reducing the risk of birth defects)</p> <p>[→http://www.iss.it/binary/acid2/cont/raccomandazione.pdf (in Italian)]</p> <p><i>Acido folico. prove di efficacia e considerazioni utili per la riduzione del rischio di malformazioni congenite (Folic acid. Evidences and considerations relevant to the reduction of the risk of congenital malformations.). bollettino d'informazione sui farmaci. anno xi, n. 2, pp. 66-75, 2004 (In Italian)</i></p> <p>[→http://www.iss.it/binary/acid2/cont/aifa_200402.pdf]</p> <p>Istituto Superiore di Sanità (National Institute of Health - Technical and scientific public body of the Italian national health service)</p>
Latvia	No	year not specified	<p>References not available</p> <p>Latvian association of gynaecologists and obstetricians.</p>
Lithuania	Yes	2006	<p>http://tar.tic.lt/ (website not available)</p> <p>Ministry of Health of the Republic of Lithuania</p>
Malta	Not applicable	Not applicable	<p>In 1994, Malta issued dietary recommendations in the form of a Department of Health Circular which advised pregnant women and women planning pregnancy to increase intake of food rich in folate (no url available)</p> <p>Recently (in 2013) Malta Ministry of Health edited a booklet (“Nutrition in Pregnancy”) recommending “<i>Folic acid supplementation should be started 3 months before pregnancy on the advice of your doctor</i>”</p> <p>[→ https://ehealth.gov.mt/healthportal/health_promotion/library/publications.aspx]</p>
Netherlands	Yes	1993	<p><i>Gezondheidsraad/ Voedingsraad (1993). Vervolgadvies inzake foliumzuurvoorziening in relatie tot neuraalbuisdefecten (Continued advice concerning folic acid use in relation to neural tube defects). Den Haag, Voorlichtingsbureau van de Voeding (in Dutch)</i></p> <p>Ministry of Health Welfare and Sports</p>

Box 1. Recommendations for FA supplementation in Europe			
Norway	Yes	1998	<p><i>Anbefalinger og virkemidler for økt folatinntak blant kvinner i fertil alder (Recommendations and measures to increase folic acid intake among women of childbearing age) . Rapport nr. 1/1998. Oslo:Statens ernæringsråd, 1998 (in Norwegian)</i></p> <p><i>Retningslinjer for svangerskapsomsorgen. Sosial- og helsedirektoratet (Guidelines for pregnancy care. Norwegian Directorate of Health) 2005. ISBN 82-8081-067-6 (in Norwegian)</i></p> <p><i>Information on pregnancy and diet/vitamins [→ http://helsenorge.no/Helseogsunnhet/Sider/Mat-og-drikke/Vitaminer-og-mineraler.aspx (in Norwegian)]</i></p> <p>Norwegian Directorate of Health</p>
Poland	Yes	1997	<p><i>Brzeziński Z. Primary prevention program for neural tube defects in Poland [Article in Polish] Med Wieku Rozwoj. 1999 Oct-Dec;3(4):503-8.</i></p> <p>National Research Institute of Mother and Child (NRIMC)</p>
Portugal	Yes	1998 (last updated 2006)	<p>Clinical practice guideline number 2/DSMIA (1998 - updated 2006)</p> <p>General Directorate of Health</p>
Rep. of Moldova	Yes	2001	<p><i>National Guide on Perinatology (ed. by P. Stratulat, 2001)</i></p> <p>Scientific Research Institute of Motherhood and Childhood Health Care</p>
Slovenia	No	1998	<p><i>Pušenjak S, Salobir.Gajšek U, Novak-Antolič Ž, Tul N. Preprečevanje nepravilnosti v razvoju nevrnalne cevi pri plodu (Prevent irregularities in the development of neural tube in the fetus). Zdrav Vars 1998;11:521-22 (in Slovenian)</i></p> <p><i>Završnik S, Novak- Antolič Ž (2001) » Supplementation with folic acid prevents neural tube defects. Situation in Slovenia« Preterm labour, delivery and newborn: proceedings / VIII. Novakovi dnevi, Maribor; editor Živa Novak –Antolič. Association for Perinatal Medicine. 177-184</i></p> <p><i>Farkaš Lainščak J, Novak Antolič Ž, Hiastan ribič C, Zaletel Kragelj L. Public health perspectives of the prevention of neural tube defects with folic acid. ZDRAVSTVENO VARSTVO 48 (2): 68-77</i></p> <p>Slovenian Association for Perinatal Medicine</p>
Spain	Yes	1992 (last update, 2003)	<p><i>Recomendaciones sobre suplementación con ácido fólico para la prevención de defectos del tubo neural (Recommendations on Folic acid supplementation to prevent neural tube defects). Información Terapéutica del Sistema Nacional de Salud (in Spanish): 1st 1996 Vol.20: 91-92</i></p>

Box 1. Recommendations for FA supplementation in Europe

			<p>2nd 1998 Vol.22:150-151</p> <p>3th 2001.Vol.25:66-67</p> <p><i>Guía para la prevención de defectos congénitos (Guidelines for prevention of birth defects) (2006) (in Spanish)</i> [→http://www.msps.es/profesionales/prestacionesSanitarias/publicaciones/docs/GuiaPrevencionDDCC.pdf]</p> <p><i>El embarazo: una nueva etapa de la vida (Pregnancy: a new step of life) (in Spanish)</i> [→http://www.sp.san.gva.es/DgspPortal/docs/embarazoNuevaEtapaVida_cas.pdf]</p> <p>Ministry of Health</p>
Sweden	Yes	1996 (last update, 2001)	<p><i>Socialstyrelsen. Meddelandeblad Nr.8. Aktuellt i folsyrafrågan (Current information in the folic acid question); 1996. (in Swedish)</i></p> <p><i>Socialstyrelsen. Meddelandeblad Nr 1. Folsyra i samband med graviditet (Folic acid in pregnancy); 2001. (in Swedish)</i></p> <p>National Board of Health and Welfare</p>
Switzerland	Yes	1996 (last update, 2002)	<p><i>Tönz O., Lüthy J., Raunhardt O (1996), Folsäure zur Verhütung von Neuralrohrdefekten (Folic acid for the prevention of neural tube defects). Schweiz Med Wochenschr, Vol 126, pp 177-187. (in German)</i></p> <p><i>Tönz O., Lüthy J (1996), Folsäure zur primären Verhütung von Neuralrohrdefekten (Folic acid for the primary prevention of neural tube defects). Bulletin des Médecins Suisses, Vol 77, No 14, pp 569-572 (in German)</i></p> <p><i>Eichholzer M., Lüthy J., Moser U., Stähelin H.B., Gutzwiller F (2002), Sicherheitsaspekte der Folsäure für die Gesamtbevölkerung (Safety aspects of folic acid for the total population). Praxis, Vol 91, pp 7-16 (in German)</i></p> <p><i>Baerlocher K., Eichholzer M., Lüthy J., Moser U., Tönz O.: Acide folique: Rapport d'experts de la commission fédérale d'alimentation sur la prophylaxie des anomalies du tube neural (Folic Acid: Expert Report of the Federal Power Commission on the prevention of neural tube defects.). Office fédéral de la santé publique, Berne 2002, 73p (in French)</i></p> <p>Federal Office of Public Health</p>
UK	Yes	1992	<p><i>Department of Health, Folic Acid and Neural Tube Defects: Guidelines on Prevention, Department of Health Directive PL/CMO (1992) 18 London HMSO</i></p> <p>Department of Health in conjunction with the Scottish Office, the Welsh Office and the Northern Ireland office</p>
Ukraine	Yes	2002 (last update, 2011)	<p><i>Order No. 417 "On Improvement of Outpatient Obstetric-gynecologic Aid in Ukraine", Ministry of Health Care of Ukraine, July, 15, 2011: "Recommended daily intake 400 mcg FA before pregnancy and early in pregnancy (till 12 weeks gestation) for NTD prevention in fetus."</i></p> <p>Ministry of Health Care of Ukraine</p>

Box 2. Recommendations of FA supplementation: target population

(in quotation marks the words used by survey respondents or quoted in the EUROCAT and EFSA report to describe the content of FA recommendation)

	women of childbearing age	women planning pregnancy		women of childbearing age	women planning pregnancy
Austria	---	Yes	Lithuania	---	---
	<i>"all women wishing to become pregnant" (EurocatReport)</i>			<i>"pregnant women in first trimester of pregnancy" (SurveyRespondent)</i>	
Belgium-Flanders region	Yes	No	Malta	Not applicable	Not applicable

Croatia	Not applicable	Not applicable	Netherlands	---	Yes
				<i>"all women wishing to become pregnant" (EurocatReport)</i> <i>"women wishing to conceive" (EfsaReport)</i>	
Czech Republic	Yes	Yes	Norway	---	Yes
	<i>"women who could or plan to become pregnant" (SurveyRespondent)</i>			<i>"women who are planning a pregnancy or who may become pregnant" (EurocatReport)</i> <i>"Women planning to become pregnant" (EfsaReport)</i>	
Denmark	---	Yes	Poland	Yes	Yes
	<i>"women planning a pregnancy" (EurocatReport)</i> <i>"women planning to become pregnant" (EfsaReport)</i>			<i>"women of childbearing age, including those planning a pregnancy" (EurocatReport)</i>	
Estonia	Not applicable	Not applicable	Portugal	---	Yes
				<i>"at least two months before stopping contraception" (EurocatReport)</i>	
Finland	---	Yes	Republic of Moldova	---	---
	<i>"all women planning a pregnancy" (EurocatReport)</i>			<i>"pregnant women during first 12 weeks of pregnancy"</i>	
France	---	Yes	Slovenia	---	Yes
	<i>"women planning a pregnancy" (EurocatReport)</i> <i>"women planning to become pregnant" (EfsaReport)</i>			<i>"all women wishing to become pregnant" (EurocatReport)</i>	
Germany	Yes	Yes	Spain	---	Yes
	<i>"women planning a pregnancy" (EurocatReport)</i> <i>"women who wish or could become pregnant" (EfsaReport)</i>			<i>"all women who are considering a pregnancy" (EurocatReport)</i>	
Hungary	---	Yes	Sweden	---	---
	<i>"Women planning a pregnancy" and "during the preparation for pregnancy" (EurocatReport)</i>			<i>"women who are planning a pregnancy or who may become pregnant" (EurocatReport)</i> <i>"women of fertile age" (EfsaReport)</i>	
Ireland	Yes	---	Switzerland	---	---
	<i>"if there is any possibility of pregnancy" (EurocatReport)</i> <i>"women of childbearing age who are sexually active" (Efsa Report)</i>			<i>"all women of childbearing age without safe contraception" (EurocatReport)</i> <i>"all women of childbearing age without safe contraception" (EfsaReport)</i>	
Italy	Yes	Yes	UK	Yes	Yes
	<i>"all fertile women that plan a pregnancy or do not actively exclude the possibility" (EurocatReport)</i> <i>"women planning or not actively excluding a pregnancy" (Efsa Report)</i>			<i>"when trying to conceive" (SurveyRespondent)</i> <i>"all women contemplating pregnancy" "planning a pregnancy" EurocatReport)</i> <i>"women who could become pregnant or are planning a pregnancy"(EfsaReport)</i>	
Latvia	---	Yes	Ukraine	---	---
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Box 3. Governmental Support and Facilities: additional details about full or partial reimbursement of FA supplement to prevent CA

Croatia - The WP7 Survey respondent (Dr Ivo Baric) answered "Women can get FA as a prescribed drug free of charge...at dose of 5mg" . In the EUROCAT Special Report 2009 the author from Croatia (Dr. Visnja Tokic, Ingeborg Barisic and Romana Gjerjaj)reported "there is no funding for FA products during pregnancy; pregnant women have to pay for it themselves".

Finland - The WP7 Survey respondent (Dr Annukka Ritvanen) answered "The 4 mg supplementation always needs a receipt and is thus nationally partially reimbursed. The vitamin tablets containing 0,4 mg are not reimbursed."

France - In the EUROCAT Special Report 2009 the author from France (Dr. Janine Goujard and Elisabeth Robert-Gnansia) reported "The ministry of health agreed to refund women for 65% of the cost for these tablets (0,4 mg) when they are prescribed to prevent malformations"since 2003 .

Ireland - In Ireland, 36% of the population receive free medical services (Primary Care, Hospital care, prescriptions) - they have access to a 'Medical Card'. A medical Card is given to people who have socio-economic difficulties or some types of chronic illness. The remaining 64% of people have to pay for their prescriptions including folic acid and they are not reimbursed. Ireland official leaflet reports following explanation regarding FA supplement cost "If you have a medical card, you can get them free of charge on prescription from your doctor."

Italy – There are two 0,4 mg FA products (fertifol and folidex). These tablets are exclusively indicated for NTD primary prevention in women planning pregnancy. They are fully reimbursement by National Health Systems since 2004. The 5 mg FA product (named Folina) was reimbursable only for patients with megaloblastic anemia due to dietary folate and vitamin B12 deficiency (until 2010) . Since July 2011 this product is free of charge for all population including women with increased risk of having NTD (women with previous NTD affected pregnancy, with diabetes, with epilepsy etc).

Malta - The WP7 Survey respondent (Dr Miriam Gatt) answered "In Malta folic acid supplementation is not offered routinely free of charge to healthy women planning on or becoming pregnant. Folic acid is given to women free of charge only if there is associated a pathology (e.g. epilepsy)."

Spain – A WP7 Survey respondent (Dr Carmen Martos) reported "Yes, currently" specifying "During the pregnancy follow-up and in family planning unit". Another WP7 Survey respondent (Dr. Martinez Frias and Dr. Bermejo-Sánchez) provided information about "several preparations for which women only pay a part of their cost". The WP7 Survey respondents (Dr Isabel Portillo and Blanca Gener)reported "The price...is 60% subsidized by the Health System".

Sweden- In the EUROCAT Special Report 2009 the author from Sweden (Dr Goran Anneren and Birgitta Ollars) reported "In the September 2007, the Board of the National Food Administration made the strategic decision to distribute FA supplements free of charge to women in the range 18-45 years"

UK – A WP7 Survey respondent (Dr Judith Rankin) reported "Pregnant women do not have to pay for prescriptions in the UK so can get it free on prescription but would have to pay for it themselves to take before conception". The WP7 Survey respondent for Wales reported "Free prescription drugs in Wales since 2003". By our research results that: "If you are on a low income, or are under 18, you may be able to get vitamin supplements containing FA free of charge. This is part of the government's healthy start scheme" (<http://www.healthystart.nhs.uk/food-and-health-tips/vitamins/>).

Box 4. Overview of the EU Regulations on fortified foods

The proliferation in the production and use of voluntary fortified foods and dietary supplements has required regulation of these products to ensure the safety of the whole European population from unacceptably high intakes. Regulation is needed, for example, to define which chemical form of a nutrient is allowed in these products and the amount of a nutrient that can be added. **Regulation EC No 1925/2006** came into force at the end of 2006 [European Commission (2006) Regulation EC No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods. Official J EC L 404, 26–38]. It is a proposal for a regulation on the addition of vitamins and minerals to foods with a view to harmonizing legislation throughout member states of the EU. It deals with vitamins and minerals added to foods other than food supplements (which are covered by Directive 2002/46/EC). The Regulation specifies foods that may not have added vitamins and minerals, notably beverages containing more than 1.2 % by volume of alcohol and unprocessed food such as fruit, vegetables, meat, poultry and fish. Only vitamins and/or minerals listed in Annex I, in the forms listed in Annex II, may be added to foods. Folic acid is listed in annex I and only pteroylmonoglutamic acid is specified in Annex II as vitamin formulation which may be added to foods. Regulation EC No 1170/2009 amending Regulation EC No 1925/2006, modifying Annex II list. The new list include calcium-L-methylfolate as folic acid formulation.

In the last ten year consumers are increasingly interested in the information appearing on food labels. They have also become more interested in their diet, its relationship to health, and, more generally, the composition of foods that they are selecting. For these reasons it is important that information about foods and their nutritional value appearing on the labelling and used for their presentation, marketing and advertising should be clear, accurate and meaningful.

The food industry has responded to the increased interest of consumers in nutrition by providing nutrition labelling on many fortified end no-fortified foods and by highlighting the nutritional value of products through claims in their labelling, presentation and advertising.

In December 2006 EU decision makers adopted a **Regulation EC 1924/2006** [European Commission (2006) Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods Official J EC L404: 9-25] on the use of nutrition and health claims for foods which lays down harmonized EU-wide rules for the use of health or nutritional claims on foodstuffs based on nutrient profiles. Regulation EC No 353/2008 [Regulation (EC) No 353/2008 of 18 April 2008 establishing implementing rules for applications for authorisation of health claims as provided for in Article 15 of Regulation (EC) No 1924/2006 of the European Parliament and of the Council Official J EC L 109] and subsequent amendment identify the conditions for establishing an application for authorization of health claims. Each application for authorization may only deal with one health claim. It includes a proposal for the wording of the claim and its conditions for use, as well as the scientific data which justifies it.

EFSA is responsible for verifying the scientific substantiation of the submitted claims, some of which are currently in use, some of which are proposed by applicants/companies who want to submit claims for authorization in the EU.

Following a request from the European Commission, the Panel EFSA on Dietetic Products, Nutrition and Allergies provided a scientific opinion on a list of health claims pursuant to Article 13 of Regulation (EC) No 1924/2006. Food businesses are not allowed to use rejected health claims.

According Regulation EC 1924/2006 claims fall into three categories:

- Art.13.1 refer to the role of a nutrient or substance in general function (growth, development and psychological functions) .
- Art. 13.5 are those based on newly developed scientific evidence and/or for which protection of proprietary data is requested.
- Art. 14 refer to the reduction of disease risk or to children's development or health.

EU has issued a “Register on nutrition and health claims” for everybody to keep himself informed about such claims (accessible clicking on

<http://ec.europa.eu/nuhclaims/>)

The EU Register gives information on:

- permitted and rejected health claims;
- the conditions of use and/or restrictions applying to permitted health claims;
- EU legal acts related to the specific health claims;
- national measures referred to in Art. 23(3) of Regulation (EC) No 1924/2006; permitted nutrition claims and the conditions for their use.

All health claims actually authorized regarding the beneficial effects of folate are related to Article 13.1. The Food Companies have limited interest to promote their products with claims under Article 14. Among the health claims permitted for folate, only one (ID 2882) empathizes “Folate contributes to maternal tissue growth during pregnancy”, referring to beneficial effects of folate on pregnancy. In this case “favourable effects on a normal pregnancy” is the proposed wording, but there are not referring to preventable effects of folate on congenital anomalies.

Others authorized health claims are related to folate contribution to normal “blood formation”, “homocysteine metabolism”, “cell division”, “amino acid synthesis”, “immune system function” etc.

In 2013 an application proposed the following wording for the health claim: “Folic acid supplementation raises maternal red blood cell folate. Low maternal red blood cell folate is a risk factor for neural tube defects in the developing foetus” pursuant to Article 14 of Regulation (EC) No 1924/2006 (health claim referring to disease risk reduction). The EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to increasing maternal folate status by supplemental folate intake and reduced risk of neural tube defects (NTD). *[EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) (2013). Scientific Opinion on the substantiation of a health claim related to increasing maternal folate status by supplemental folate intake and reduced risk of neural tube defects pursuant to Article 14 of Regulation (EC) No 1924/2006 EFSA Journal 2013;11(7):3328]*

The Panel considers that:

- the food constituent, supplemental folate, which is the subject of the claim, is sufficiently characterised;
 - the target population is women of child-bearing age;
- the increasing maternal folate status by supplemental folate intake is a beneficial physiological effect in the context of reducing the risk of neural tube defects;
- the following wording reflects the scientific evidence: “Supplemental folate intake increases maternal folate status. Increasing maternal folate status contributes to the reduction of the risk of NTD.” Furthermore the Panel remarks that in order to obtain the claimed effect 400 µg supplemental folate should be consumed daily for at least one month before and up to three months after conception.

Box 5. Overview of the EU Regulations on classification, labelling and packaging of chemicals and mixtures

The EU incorporated United Nations Globally Harmonized System (GHS) on classification, labeling and packaging of chemicals and mixtures in 2008. The EU has implemented the GHS particularly for industrial chemicals, applying a mandatory approach by gazetting the EU Regulation 1272/2008 (*Draisci R, 2011*). This Regulation, also known as the 'CLP Regulation', gradually came to replace previous European legislation on the classification, labelling and packaging of chemicals in the EU and it is now applicative in all EU member states (*Di Prospero et al, 2011*).

The EU, with the gazetting of EU regulation 1272/2008, is successfully incorporating GHS elements chemical classification and labelling as regional mandatory requirements (*Ta GC et al, 2011*).

Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC and amending Regulation (EC) No 1907/2006.

The risk-phrase (R-phrases) relevant for reprotoxic agents (as defined in previous regulation) was the followings:

- R46- may cause heritable genetic damage;
- R60- may impair fertility;
- R61- may cause harm to the unborn child;
- R62- Possible risk of impaired fertility;
- R63- Possible risk of harm to the unborn child.

Under CLP regulation, these risk phrases (R-phrases) are replaced by the following "Hazard statements" (standard phrases assigned to a hazard class -H-and category):

- H340: May cause genetic defects;
- H341: Suspected of causing genetic defects;
- H360: May damage fertility or the unborn child;
- H361: Suspected of damaging fertility or the unborn child.

The CLP Regulation introduces a new specific "Precautionary Statement" advice for adequate preventive measures during pregnancy:

- P263: Avoid contact during pregnancy/while nursing