Methods used in the Modell Database of Congenital Disorders (MGDb)

1. Introduction. Scope and general concepts

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# Abstract

Congenital disorders (often also called birth defects)[[1]](#footnote-1) are “any potential pathological conditions arising before birth --- whether they are evident at birth or become manifest later in life” (WHO 1985a, 2000, 2006; Malherbe et al 2023). The Modell Database of Congenital Disorders (MGDb) is designed to generate evidence-based country-specific estimates of their birth prevalence and outcomes and make them publicly available.

There are two main groups of congenital disorder: (1) Environmental congenital disorders due to maternal exposure to infection or other (preventable) hazards: it is difficult to quantify their global burden because their prevalence varies with time and place; (2) Congenital disorders with mainly endogenous causes - chromosomal disorders, congenital malformations, single gene disorders and disorders due to common genetic risk factors. The MGDb combines (a) the fact that the baseline birth prevalence[[2]](#footnote-2) of this groupis relatively constant in any given population and, (b) evidence that 60-70% of adverse outcomes can be avoided with equitable access to available interventions, to generate global, regional and country-specific estimates of the birth prevalence and outcomes of severe early-onset endogenous congenital disorders.

In summary, the MGDb estimates that in 2021 there were over 3.5 million births with a severe endogenous congenital disorder, over 350,000 attributable fetal deaths, around 1.8 million under-5 deaths and over 2 million survivors with disability at 5 years of age. These estimates are considerably higher than those of the Global Burden of Disease (GBD) study and the WHO’s Global Health Estimates (GHE): the comparison deserves further investigation.

The MGDb does not pretend to provide accurate figures. The provisional, but evidence-based estimates are intended to provide a starting point for assessing the burden of congenital disorders and the power of interventions in countries where observational data are insufficient to support local policy-making.

# Introduction

Congenital disorders (birth defects) are “any potential pathological conditions arising before birth --- whether they are evident at birth or become manifest later in life” (WHO 1985a, 2000, 2006; Malherbe et al 2023). Figure 1 shows the main groups of disorder that fall within this definition.



Figure 1. The main groups of congenital disorder. The image is notional: there is no relation between birth prevalence and size of the circles or extent of overlap between categories. The MGDb currently includes only early-onset congenital disorders whose birth prevalence is relatively constant or can be calculated, namely chromosomal disorders, non-genetic congenital malformations, single gene disorders and two common disorders due to genetic risk factors - rhesus haemolytic disease of the newborn and neonatal jaundice due to glucose-6-phosphate dehydrogenase deficiency.

Congenital disorders can affect any aspect of **structure** or **function** and cover a wide range of severity. Severe congenital disorders, defined as those that usually cause death or disability in the absence of intervention, are an important cause of early death and life-long disability. Their burden can be greatly reduced by available interventions, but diagnosis often requires clinical and laboratory facilities that are only available in high income settings. The consequent shortage of reliable local epidemiological data on the birth prevalence and outcomes of congenital disorders in much of the world has led to serious under-estimation of their public health importance and impedes the development of policies for their prevention and care.

We propose that this problem can be largely overcome because the birth prevalence of four major disorder groups is largely determined by endogenous causes and so is relatively constant for any given population in the absence of intervention before or during pregnancy. That is, they have a predictable *baseline birth prevalence2*. The baseline birth prevalence of most *non-genetic* *congenital malformations* is broadly similar worldwide; that of common *chromosomal disorders* is predictably related to maternal age, and that of *rare single gene disorders* is predictable from the basic principles of population genetics, including the effect of parental consanguinity. In addition, sufficient country-specific data exist on the baseline birth prevalence of neural tube defects and oro-facial clefts, and the carrier prevalence of haemoglobin disorders, rhesus negativity and G6PD deficiency to enable country-specific calculations. Consequently, these groups may be collectively called *endogenous congenital disorders.*

## Disorder groups included in the MGDb

The MGDb includes estimates for the birth prevalence and outcomes of the following groups of severe endogenous early-onset disorders.

* Chromosomal disorders: Down syndrome, other trisomies, rare chromosomal disorders, Turner syndrome and Klinefelter syndrome.
* Non-genetic (and isolated) congenital malformations: anencephaly, spina bifida and encephalocele, oro-facial clefts, congenital heart disease, other severe malformations, less severe malformations (limb and genitalia)
* Two common disorders due to genetic risk factors: rhesus haemolytic disease of the newborn and neonatal jaundice due to G6PD deficiency.

## The importance of the baseline birth prevalence

The availability of a baseline birth prevalence is an unusual, and possibly unique characteristic of endogenous congenital disorders. It offers exceptional advantages to epidemiologists and other relevant stakeholders because once it is known, it can be related to available demographic and survival data and the observed effects of interventions to reach country-specific estimates of the distribution of outcomes including pre-pregnancy prevention, termination of pregnancy, fetal death, under-5 death, disability, and cure. Furthermore, the sum of these outcomes must fill (or equal) the original “envelope” of baseline birth prevalence. That is, this type of disorder can be handled as a closed system. The MGDb exploits this exceptional characteristic to generate evidence-based estimates of the birth prevalence and outcomes of endogenous congenital disorders for use in service planning. Tables of country regional and global key outputs are available in the LSHTM repository.

The epidemiological methods specific to congenital disorders developed for the MGDb are simple enough to be used by non-specialist health professionals.[[3]](#footnote-3) This article provides a general introduction. All the estimates mentioned here are supported in the remaining topic- or disorder-specific articles in this series and their annexes.

*We emphasise that the MGDb does not pretend to provide accurate figures. Rather, it offers a framework for assessing the burden of endogenous congenital disorders and generates provisional but evidence-based estimates intended to fill the void caused by the absence of observational data and so help remove the impasse to policy and service development that often results.*

## The need for consensus on a terminology for congenital disorders

Poorly defined terminology caused many difficulties in developing the MGDb. It was therefore necessary to define a set of terms that are sufficiently precise to enable quantitative estimates. The definitions offered in *Article 1.1 Terminology* are used throughout this series of articles.

It is not proposed that these terms should be universally adopted. They were developed specifically for use in Community Genetic epidemiology and some may not be acceptable to some specialists. We present them here in the hope of encouraging consultation and movement towards a consensus.

## The place of environmental congenital disorders

The MGDb does not currently include congenital disorders caused by environmental risk factors such as maternal infection, malnutrition, or exposure to teratogens because their baseline birth prevalence varies with place, time, and the deployment of interventions. Ongoing surveillance or periodic surveys are therefore required but insufficient country- and time-specific observational data are available from the countries where they are most prevalent to permit the form of modelling used in the MGDb. Should sufficient data become available their inclusion may be considered in the future.[[4]](#footnote-4)

This exclusion does not detract from the relevance of environmental congenital disorders. They have high priority in WHO recommendations for pregnancy care because affected births can be largely prevented by basic public health interventions including sanitation, immunisation, nutritional supplementation, restriction of exposure to teratogens, and diagnosis and treatment for the mother before or during pregnancy (WHO 2013a, 2013b). The discussion therefore includes a very provisional attempt to grasp their present birth prevalence and outcomes.

The distinction between environmental and endogenous congenital disorders used in the MGDb is not absolute: some disorders classed as endogenous are also strongly influenced by environmental factors, and environmental influences usually interact with genetic predispositions[[5]](#footnote-5). Rather, as is common in clinical medicine, the distinction is pragmatic and reflects the limits of the method used.[[6]](#footnote-6)

## Historical background

The need for epidemiological data on congenital disorders was recognised in the aftermath of the second world war, when the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) was established “to collect and evaluate information on the levels and effects of exposure to ionizing radiation” (See Annex 1 and UNSCEAR 1977, 1982, 1986). Meticulous controlled studies on the prevalence of congenital disorders were conducted in the populations of Hiroshima and Nagasaki at this time on the assumption that increased mutation would manifest as an increased birth prevalence of affected children (Schull and Neel 1956, Schull et al.1981, Schull 2003)[[7]](#footnote-7).

In the 1960s a combination of increasing technical diagnostic ability, the observed effects of rubella infection and the thalidomide tragedy led to increased recognition of the contribution of congenital disorders to early death and disability, the potential power of interventions, and the need for ongoing surveillance. Accordingly, the World Health Organisation (WHO) encouraged epidemiological studies, the development of congenital anomaly registries (structural congenital disorders), and the construction of databases for common genetically-determined disorders.

### Epidemiological studies

Table 1 summarises classical studies that contributed to the estimation of the baseline birth prevalence of endogenous congenital disorders[[8]](#footnote-8) in the MGDb. These studies have the advantage that they predate the introduction of interventions that reduce affected livebirth prevalence (e.g. periconceptional vitamin supplementation, termination of pregnancy for fetal impairment) or increased detection rates (e.g. routine fetal anomaly scanning, sophisticated neonatal screening). Although the range of diagnoses included differed between studies, and most studies were conducted in populations of European origin, the rates observed were broadly consistent and were generally considered to apply world-wide (Baird et al. 1988). These early estimates are especially valuable because of their timing. The introduction of interventions such as folic acid food fortification, genetic carrier screening and genetic counselling, and prenatal diagnosis with the option of termination of pregnancy have subsequently complicated the recording of baseline birth prevalence.

Table 1. Classical studies of the birth prevalence of congenital disorders1

|  |  |  |  |
| --- | --- | --- | --- |
| Source | Chromosomal disorders | Congenital malformations | Rare single gene disorders |
| Neel 1958 |  | + |  |
| Stevenson 1959 |  +  |  +  |  +  |
| WHO 1966 (Stevenson et al.) |  |  +  |  |
| Trimble and Doughty 1974 |  +  |  +  |  +  |
| Myrianthopoulos and Chung 1974 |  |  +  |  |
| Ash, Vennart & Carter 1977 |  +  |  +  |  +  |
| Hook and Hamerton 1977 |  +  |  |  |
| Carter 1977 |  |  |  +  |
| Czeizel & Sankaranarayanan 1984 |  +  |  +  |  |
| Baird et al. 1988 |  +  |  +  |  +  |

Note. All studies include only disorders that cause death or disability in the absence of intervention.

AC Stevenson was the first to attempt to measure “the load of hereditary defects in human populations” based on the number and age distribution of patients referred to his Northern Ireland clinic (Stevenson 1959). These estimates of birth prevalence and early mortality, made at a time when only supportive care was available, led the WHO to conduct a comparative study of the birth prevalence of selected congenital anomalies in 24 centres representing all WHO regions, to review the global prevalence and management of haemoglobin disorders, and to publish three technical reports (WHO 1966a, 1966b, WHO 1972).

### Congenital anomaly registries

Congenital anomaly registries were progressively established from the 1950s onwards. Two of the earliest have made unique contributions to global epidemiology.

* The British Columbia Health Surveillance Registry was initiated in 1952 (Baird 1987). Whilst most congenital anomaly registries include only disorders associated with structural change (the “*congenital malformations, deformations and chromosomal disorders*” included in chapter XV11 (the Q chapter) of ICD10) this registry also included rare single gene disorders: the reported birth prevalences remain relevant today and are used in the MGDb. The group also conducted survival studies. Their meticulous data for Down syndrome are also used in the MGDb.
* The national Hungarian Congenital Abnormality Registry initiated in 1962 (Czeizel 1997) was exceptional in being partnered with a public health initiative, the Hungarian Optimal Planning Programme (Czeizel 2012, Czeizel et al. 1998). This combination enabled invaluable studies including a pioneering assessment of the burden of congenital anomalies in terms of years of life lost, lived with disability or lived effectively cured (Czeizel & Sankaranarayanan 1984), estimates of the power of interventions for prevention and care (Czeizel et al. 1993), and randomised controlled trials of interventions aiming to improve birth outcomes, including pre-conceptional multivitamin or folic acid supplementation (Czeizel and Dudas 1992, Czeizel et al. 1997). The Hungarian estimates for the birth prevalence of congenital anomalies were used in the influential March of Dimes global report on birth defects (Christianson et al. 2006).

Particularly important for global epidemiology, two “umbrella registries” were initiated in 1974 to collect, standardise and harmonise data on birth prevalence and birth outcomes from individual registries and regularly publish key reference data. The European Surveillance of Congenital Anomalies and Twins network (EUROCAT, [www.eurocat-network.eu](http://www.eurocat-network.eu)) aims to record the majority of severe congenital anomalies. The International Clearing House for Birth Defect Surveillance and Research (ICBDSR, [www.icbdsr.org](http://www.icbdsr.org)) collects data from countries at all levels of development and reports on the 30-50% of congenital anomalies that can be reliably diagnosed around the time of birth in the absence of advanced facilities. These umbrella registries have the outstanding advantage that they use standardised terminology, include only severe disorders[[9]](#footnote-9) and, when feasible, report all birth outcomes (termination of pregnancy for fetal impairment, fetal death/stillbirth, live birth), and so enable quantification of the effect of interventions that affect birth prevalence or birth outcomes. These two registries are the primary sources for MGDb estimates of the baseline birth prevalence of congenital anomalies.

### Databases of genetically-determined disorders

Three pioneering enterprises contributed to a global picture of genetically-determined disorders: Livingstone’s database on haemoglobin disorders and G6PD deficiency (Livingstone 1985), Mourant and colleagues on ABO and rhesus blood groups (Mourant et al. 1976) and Alan Bittles’ collection of data on the distribution of parental consanguinity (Bittles [www.consang.net](http://www.consang.net)). Their original data together with more recent studies are used to develop MGDb estimates for haemoglobin disorders, rare single gene disorders, rhesus haemolytic disease of the newborn and neonatal jaundice due to GDPD deficiency.

### Developing the principles of Community Genetics

In the early 1980s Anver Kuliev, director of the WHO Hereditary Diseases programme, identified three key components of Community Genetics - epidemiology, audit of the effect of interventions (surveillance), and information and education (WHO 1985) and initiated development of a global epidemiological picture, starting with country-specific estimates for haemoglobin disorders (WHO 1983) and G6PD deficiency (WHO 1985b). The work continued in collaboration with the WHO regional offices for Europe (EURO) (Modell et al. 1992) and the Eastern Mediterranean (EMRO) (Alwan and Modell 1997, Christianson and Modell 2004), supported by the Wellcome Trust to 2000 and then by EMRO. The estimates contributed to several WHO reports (WHO 2000, 2006), provided the quantitative basis for the influential MOD (March of Dimes) Global Report on Birth Defects (Christianson et al. 2006) and contributed estimates for the “Born Healthy” needs assessment toolkit (Nacul et al. 2013: <http://www.bornhealthy.org>).

Following WHO endorsement of the MOD estimates (WHO 2006) the World Health Assembly approved a Declaration on Birth Defects including the recommendation *“to promote the collection of data on the global burden of mortality and morbidity due to birth defects” and “resolve currently divergent opinions on the health burden of both environmental and endogenous birth defects”* (WHO 2010, see Annex 2).

Following the MOD report the Global Burden of Disease study commissioned Professor Joy Lawn to convene an Expert Group on Congenital and Genetic Disorders. The group approved the MOD birth prevalence estimates and promoted further development of the database, in response to the World Health Assembly declaration, to include estimates of early death disability and cure.[[10]](#footnote-10) The current MGDb is the outcome of this collaboration.

# The general method

Baseline birth prevalence - affected births that would occur in the absence of any intervention[[11]](#footnote-11) - provides the foundation of the MGDb. MGDb estimates of baseline birth prevalence are in general strongly evidence-based, though some under-ascertainment is probable.

The MGDb generates estimates for all birth outcomes from 20 weeks’ gestation onwards.[[12]](#footnote-12) Crucially, all must fit into the envelope provided by baseline birth prevalence.

Figure 2 shows the possible outcomes for a severe congenital disorder in the baseline “no-care” situation.



Figure 2. In the absence of intervention – the “no-care” or baseline situation - the only possible outcomes for a severe congenital disorder are miscarriage, stillbirth, early death or disability.

Quantitative estimates of “no-care” outcomes are based on classical early studies from high income countries, on rare local studies, or on expert opinion when no such reports are available.

Figure 3 indicates the possible points for intervention, with additional outcomes shown in red. Interventions included in the MGDb are: administration of anti-D to rhesus negative women; mandatory folic acid food fortification; genetic risk assessment and counselling; prenatal diagnosis with the option of termination of pregnancy; and early diagnosis and care.



Figure 3. Chart showing the sequence of events covered in the MGDb. Blue lines show outcomes in the absence of intervention. Red lines show possible interventions and their main outcomes.

Estimates of outcomes with “100% access to services” are based on observational data from high income settings where available interventions are equitably deployed at the population level. However inter-country differences in policies for deployment of e.g. folic acid food fortification or the option of termination of pregnancy must also be considered.

## Assessing the power of interventions

In the MGDb, Western Europe is used as a *global reference region* because most of the population has equitable access to services and outcomes are recorded through congenital anomaly registries and targeted research studies. Outcome estimates for this reference region are therefore strongly evidence-based and may be taken to represent the effect of 100% access to services at the population level. That is, they represent the “power” of available interventions when fully deployed.[[13]](#footnote-13)

## Achieving country-specific estimates of outcomes

It is assumed that most outcomes in high income countries will be close to those estimated for 100% access to services, while outcomes in very low-income settings will be close to those in the no-care situation. Estimates for countries that lie between these two extremes are obtained by (a) estimating the proportion of the population with access to relevant services, using infant mortality as an indicator, and (b) relating the result to outcomes with no care and 100% access to services. The resulting rates are then applied to World Population Prospects (WPP) country-specific demographic data to estimate annual affected births and early deaths, survivors cured or living with disability, past and present numbers of living patients, and potential future effects of policy changes.

So that the estimates may be used with confidence in policy-making, great care is taken throughout to avoid over-estimation.

There is considerable uncertainty in the assessment of outcomes because estimates are only as accurate as the input data permit. For example, there is probably under-estimation of termination of pregnancy, and of current survival in high income settings because survival studies inevitably lag behind current practice. Such errors would lead to over-estimation of early mortality and under-estimation of survival with disability or cure. However, the effect on total adverse outcomes is limited because an error in estimating one outcome simply shifts cases into other outcomes within the same envelope.

## Instruments and resources developed to enable production of estimates

The aims of the MGDb are (a) to provide country-specific order-of magnitude estimates that can be used to support policy-making when there is a shortage of observational data and (b) to encourage local public health officials, policy makers and their expert advisors to generate their own estimates for comparison. These aims generate the following general rules.

* The method used must be as simple and reproducible as possible.
* It should depend on data sources that are as few and as authoritative as possible and ideally web-based – i.e. it should build on comprehensive datasets assembled by others.[[14]](#footnote-14)
* Key target groups (public health and primary care) are concerned primarily with bundles of care rather than single issues. Therefore, the numerous, mostly rare congenital disorders, must be aggregated into manageable groups with similar clinical features, and outcomes should be described in terms relevant to public health, such as effect of interventions on mortality, disability, and service need.
* It is not an option to omit an estimate because there are no data. Since the aim is to produce global estimates, every cell in the database must be filled for every country, even (indeed especially) when no observational data are available. In such cases an estimate must be made that is as evidence-based as reasonably possible.[[15]](#footnote-15)
* For most countries the estimates generated can only be approximations.

The equations and standard tables listed below were developed while building the Database. These instruments were made as simple as possible to facilitate comparable epidemiological assessment world-wide.

#### Equations for calculating:

* + The proportion of the population with access to specialist (secondary) services, based on infant mortality rate.
	+ The birth prevalence of Down syndrome and other trisomies: from the per cent of mothers aged 35 or over.
	+ The effect of parental consanguinity on the collective birth prevalence of recessive disorders.
	+ The potential effect of genetic counselling on the birth prevalence of single gene disorders.
	+ The effect of folic acid food fortification on the birth prevalence of folate-sensitive congenital malformations.

#### Generally-applicable tables of:

* + Baseline birth prevalences of isolated congenital malformations (other than neural tube defects and oro-facial clefts) and rare, early-onset single gene disorders.
	+ Per cent survival and estimated mean life expectancy in the absence of care and with 100% access to services, by disorder group.
	+ EUROCAT and ICBDSR rates for termination of pregnancy for congenital anomalies. These are used in estimating the effect of access to prenatal diagnosis, taking account of reported legality termination of pregnancy for fetal impairment and (as far as possible) other factors influencing this choice.

#### Country-specific tables of:

* + Baseline birth prevalence of neural tube defects and oro-facial clefts (before folic acid food fortification).
	+ Prevalence of parental consanguinity, expressed as coefficient of consanguinity.
	+ Baseline birth prevalence of haemoglobin disorders.
	+ Risk of rhesus haemolytic disease of the newborn, and of G6PD deficiency neonatal jaundice.

The development and use of each instrument is fully described in the relevant articles in this series.

## Limitations of the MGDb

The MGDb includes only early-onset[[16]](#footnote-16) endogenous congenital disorders in the groups shown in Figure 1. It does not (yet) include disorders with onset in adult life (e.g. bicuspid aortic valve, family cancer syndromes, neurodegenerative disorders, haemochromatosis); functional disorders without a known cause (e.g. blindness, deafness, cerebral palsy originating before birth); disorders caused by maternal exposure to environmental risk factors (infection, malnutrition, teratogens).[[17]](#footnote-17) Importantly, it does not include estimates for the effect of non-governmental support organisations that target specific congenital disorders.[[18]](#footnote-18)

# Some examples of outputs

The following charts illustrate the basic premise and the potential of the method used.

Figure 4 shows estimated baseline birth prevalence of the main disorder groups by WHO region. The total height of the bars represents the envelope of baseline birth prevalence.



Figure 4. Endogenous congenital disorders. Estimated baseline birth prevalence (rate /1,000 live births) by disorder group and WHO region. This is the prevalence that would prevail in the absence of any intervention. WHO regions in descending order of total prevalence.

The baseline birth prevalences of chromosomal disorders and congenital malformations are broadly similar world-wide: single gene disorders and disorders due to genetic risk factors account for most differences in collective baseline birth prevalence.

A range of interventions, detailed below, reduce affected birth prevalence, and increase the range of possible outcomes. However, the actual impact of these interventions depends on the proportion of the population with access to specialist services. Access is estimated using an equation based on infant mortality (see *Article 5*): 100% access is defined as access to specialist services currently available in Western Europe. Figure 5 shows the evolution of estimated access by WHO region.



Figure 5. Estimated evolution of access to specialist services by WHO region.

Figure 6 shows global estimates of outcomes of endogenous congenital disorders with (a) no care, (b) estimated access in 2020-24 and (c) 100% access to care (as Western Europe).



Figure 6. Endogenous congenital disorders. Estimated global outcomes with no care, 100% access to care, and with estimated access in 2020-24.

The difference between outcomes in with no care and with 100% access to care demonstrates the power of available interventions when fully deployed at the population level. Available interventions have reduced adverse outcomes by 65% in Western Europe, compared with a global estimate of 24%.

Figure 7 shows the residual perceived global health burden in the three different situations.



Figure 7. Endogenous congenital disorders. Estimated adverse outcomes with no care, 100% access and 2020-24.

The MGDb estimates for congenital anomalies and single gene disorders have the strongest evidence base. Tables 2 and 3 show global estimates of their baseline birth prevalence and attributable under-5 deaths in 2020-24.

Table 2. MDG 2020-24. Global estimates of baseline birth prevalence of congenital anomalies and single gene disorders, and attributable under-5 mortality. Rates /1,000 births.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| WHO region | Annual births, 1,000s | Under-5 MR | Baseline births /1,000 (SB & LB) | Est under-5 deaths /1,000 |
| Total congenital anomalies | Total single gene | Total CA & single gene | Total congenital anomalies | Total single gene | Total CA & single gene |
| AFR | 39,632 | 70.1 | 23.7 | 20.3 | 44.0 | 10.3 | 11.0 | 21.4 |
| AMR | 13,796 | 13.2 | 25.8 | 6.3 | 32.1 | 2.0 | 2.0 | 4.1 |
| EMR | 18,756 | 45.2 | 25.6 | 24.4 | 50.0 | 8.5 | 11.5 | 20.1 |
| EUR | 10,303 | 7.3 | 25.8 | 8.2 | 34.0 | 1.2 | 2.4 | 3.6 |
| SEAR | 33,471 | 29.1 | 25.6 | 11.0 | 36.7 | 8.5 | 5.1 | 13.6 |
| WPR | 18,004 | 11.5 | 25.5 | 6.4 | 31.8 | 2.3 | 2.1 | 4.5 |
| World | 133,962 | 37.8 | 25.1 | 14.3 | 39.4 | 7.0 | 6.8 | 13.8 |
| W Europe | 4,054 | 3.6 | 26.2 | 5.9 | 32.2 | 0.7 | 1.7 | 2.4 |

Table 3. MDG 2020-24. Global estimates of annual baseline births of congenital anomalies and single gene disorders, and attributable under-5 deaths.

|  |  |  |
| --- | --- | --- |
| WHO region | Annual baseline births | Annual under-5 deaths |
| Total congenital anomalies | Total single gene | Total CA & single gene | Total congenital anomalies | Total single gene | Total CA & single gene |
| AFR | 939,400 | 805,779 | 1,745,179 | 408,654 | 437,563 | 846,217 |
| AMR | 356,269 | 86,994 | 443,263 | 28,102 | 28,037 | 56,139 |
| EMR | 479,810 | 458,337 | 938,147 | 160,263 | 215,856 | 376,119 |
| EUR | 265,872 | 84,788 | 350,660 | 12,049 | 24,996 | 37,045 |
| SEAR | 857,921 | 369,156 | 1,227,076 | 284,659 | 170,523 | 455,182 |
| WPR | 458,261 | 114,751 | 573,013 | 42,266 | 38,262 | 80,528 |
| World | 3,357,533 | 1,919,806 | 5,277,339 | 935,993 | 915,237 | 1,851,230 |
| W Europe | 106,418 | 23,949 | 130,366 | 2,728 | 6,908 | 9,636 |

# Interventions affecting endogenous congenital disorders

Table 4 shows the main types of intervention for prevention and care of endogenous congenital disorders, their timing in relation to pregnancy, and the method used to estimate their effects. This section aims to assess their power when fully deployed and their actual current effect.

Table 4. Interventions that can reduce the burden of endogenous congenital disorders, and methods for assessing their effects.

|  |  |  |
| --- | --- | --- |
| Timing in pregnancy | Intervention | Effect of intervention based on: |
| Obligatory pre-pregnancy | Folic acid food fortification | Data on changing prevalence of neural tube defect |
| Anti-D for rhesus negative mothers | Estimated access to antenatal care |
| Genetic risk assessment and counselling | Basic population genetic theory |
| Before or during pregnancy | Carrier screening for Hb disorders | Surveillance data from established programmes |
| Genetic risk assessment and counselling | Basic population genetic theory |
| Only during pregnancy | Prenatal diagnosis (with or without the option of termination of pregnancy)Genetic counselling | Surveillance data from high income settings |
| After birth | Early diagnosis and access to therapeutic or surgical cure, supportivecare | Reported effects of care on length and quality of life |

## Estimating the power of interventions

The power[[19]](#footnote-19) of an intervention can be assessed by comparing outcomes with no care and with 100% access to services in a region with approximately equitable access and high-quality surveillance such as Western Europe. Table 5 shows estimates of the power of current interventions in this sub-region by disorder group. Collectively they result in an approximately 60% reduction in fetal deaths and more than 80% reduction in under-5 deaths due to congenital disorders. The table also shows wide differences in the effect of interventions on disability because reduced mortality often increases the proportion of survivors living with disability at 5 years of age. Furthermore, there is often a very substantial increase in the length and quality of life of these survivors.

Table 5. Estimates for Western Europe of outcomes of endogenous congenital disorders with no care, and with estimated actual care (2020-24)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Disorder group | Baseline births /1,000 | Baseline (no care) % outcomes | % outcomes if 100% access to services | Total % reduction in death and disability |
| Fetal death | U-5 death | Disabil @ 5 yr | Pre-preg reduction | TOP | Fetal death | Effective cure | Under-5 death | Disabil @ yr | Fetal death | U-5 death | Disabil @ 5 yr |
| Down | 2.98 | 14.0 | 53.7 | 33.9 |   | 56.4 | 6.1 |   | 2.3 | 35.1 | 56 | 96 | -4 |
| Other autosomal | 1.52 | 22.4 | 62.2 | 15.3 |   | 67.3 | 6.9 |  | 9.8 | 16.0 | 69 | 84 | -4 |
| Sex chromosomal | 1.12 | 6.5 | 1.1 | 92.1 |   | 14.5 | 3.5 |  | 0.7 | 81.0 | 47 | 32 | 12 |
| Severe congen malfns | 15.44 | 3.2 | 81.3 | 15.5 | 3.9 | 10.8 | 1.6 | 61.5 | 2.4 | 19.7 | 48 | 97 | -27 |
| Less severe malfns | 5.19 | 0.7 | 4.7 | 94.2 |   | 3.7 | 0.6 | 89.2 | 0.1 | 6.3 | 4 | 98 | 93 |
| Rare single gene | 5.70 | 7.0 | 57.9 | 35.0 | 4.7 | 4.2 | 6.4 |  | 29.8 | 54.7 | 8 | 48 | -56 |
| Hb disorders | 0.21 | 0 | 72.6 | 27.3 | 7.7 | 41.3 | 0.0 |  | 1.2 | 49.6 | 83 | 98 | -82 |
| Rhesus haem dis | 2.88 | 25.0 | 37.5 | 37.4 | 99.0 |  | 0.3 |  |  | 0.7 | 99 | 100 | 98 |
| G6PDd NN jaundice | 0.10 | 0 | 50.0 | 49.8 |   |  |  | 100 |  |   |   | 100 | 100  |
| Total  | 35.13 | 7.0 | 56.8 | 36.2 | 10.6 | 14.4 | 2.8 | 40.5 | 6.5 | 25.1 | 60 | 88 | 31 |

# Actual effects of interventions, 2020-24 estimates

## Folic acid food fortification

Folic acid food fortification that delivers an average of at least 100 parts per million (ppm) reduces neural tube defect birth prevalence to approximately 0.77/1,000, whatever the pre-fortification birth prevalence (Williams et al. 2015, Arth et al. 2016). The MGDb applies this general principle to estimate (a) the potential effect of folic acid food fortification and (b) its actual impact using the reported actual reach of fortification in 2017 (Kancherla et al 2018) (Table 6).[[20]](#footnote-20)

Folic acid food fortification can have an important effect even where access to health services is very limited as in AFR. The majority of preventable neural tube defects are actually prevented in AMR (where baseline birth prevalence is relatively low) but there may have been relatively little effect in SEAR where baseline birth prevalence is highest.[[21]](#footnote-21)

Table 6. Estimated baseline birth prevalence of NTD, rate /1,000 births, proportions potentially preventable and actually prevented in 2019 by WHO region (based on Kancherla et al.2018)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| WHO region | Baseline NTD /1,000 | FA prevent-able /1,000 | % FA prevent-able | NTD actually prevented /1,000 | % of NTD actually prevented | % of prevent-able NTD prevented |
| AFR | 1.42 | 0.65 | 46 | 0.55 | 39 | 84 |
| AMR | 1.44 | 0.67 | 47 | 0.74 | 52 | 111 |
| EMR | 2.92 | 2.15 | 74 | 0.53 | 18 | 24 |
| EUR | 1.48 | 0.71 | 48 | 0.14 | 9 | 20 |
| SEAR | 3.11 | 2.34 | 75 | 0.00 | 0 | 0 |
| WPR | 2.00 | 1.23 | 61 | 0.01 | 0 | 1 |
| World | 2.14 | 1.37 | 64 | 0.31 | 14 | 22 |
| W Europe | 0.89 | 0.12 | 13 | 0.000 | 0 | 0 |

*Notes*. Folic acid food fortification was/is not implemented in most of Western Europe.
The >100% estimate for prevention in AMR demonstrates the approximate nature of the calculation.

## Anti-D for rhesus negative mothers

Table 7 shows the distribution of rhesus genotypes and estimated baseline birth prevalence of rhesus haemolytic disease by WHO region. Though rhesus negativity is most common in EUR and AMR, the table shows that the baseline birth prevalence of rhesus haemolytic disease may now be higher in EMR and AFR where fertility is relatively high because the risk of rhesus haemolytic disease increases with pregnancy number (Mourant et al 1976, Bhutani et al. 2013).

Table 7. Proportion of the population with the three rhesus genotypes, and estimated baseline birth prevalence of rhesus haemolytic disease.

|  |  |  |  |
| --- | --- | --- | --- |
|  | % of the population | Total fertility rate, 2013 | Rh haemolytic disease If no intervention (2013) |
| WHO region | Rhesus negative (dd) | Heterozygous rhesus positive (dD) | Homozygous rhesus positive (DD) | Est. fetuses with sensitised mother /1,000 | Est. rhesus haemolytic disease /1,000 |
| AFR | 4 | 31 | 64 | 5.23 | 6.7 | 3.0 |
| AMR | 12 | 44 | 44 | 2.12 | 6.3 | 2.9 |
| EMR | 9 | 40 | 51 | 3.66 | 8.5 | 3.8 |
| EUR | 14 | 46 | 40 | 1.86 | 6.2 | 2.8 |
| SEAR | 4 | 30 | 66 | 2.43 | 3.2 | 1.4 |
| WPR | 1 | 13 | 86 | 1.77 | 0.5 | 0.2 |
| World | 6 | 31 | 63 | 3.08 | 4.8 | 2.2 |
|  W Europe | 16 | 48 | 36 | 1.72 | 6.5 | 3.0 |

In high income settings, rhesus haemolytic disease is practically eliminated by routine administration of anti-D to rhesus negative mothers during pregnancy and immediately after birth (Clarke 1983). It is difficult to estimate its current birth prevalence elsewhere for three reasons: (1) The accepted rate of maternal iso-immunisation is based on observations in Northern European populations but there is evidence of ethnic differences. (2) Control of rhesus haemolytic disease does not appear to be explicitly recommended in parts of SEAR and WPR. (3) Since maternity services lie somewhere between primary care and specialist services, access to care is likely to exceed the MGDb estimation of access. Nevertheless, the attempt to estimate its effect described in Article 11 (Rhesus Negativity) suggests that less than 50% of affected births may be avoided world-wide.

## Genetic risk detection and counselling

The key objectives of a genetics service are to provide accurate diagnosis, promote care for affected individuals, detect genetic risk for relatives and the general population, and provide information and counselling on managing genetic risk. The potential reach of a genetics service is therefore determined by local possibilities for genetic diagnosis and risk detection.

The ability to detect reproductive risk of single gene disorders depends on whether carriers can be identified before the birth of any affected child (prospectively) or only after the diagnosis of an affected child (retrospectively) (WHO 1966b).

### Retrospective risk detection

At present risk for most rare single gene disorders is only identified after the diagnosis of an affected child. Retrospective risk detection and genetic counselling are very valuable for the parents. However, only subsequent affected births can be avoided, so any possible effect at the population level depends on the population norm for final family size. Experience with the haemoglobin disorders shows that when a severe disorder is concerned informed at-risk couples stop further reproduction once they have one or two unaffected children. Figure 8 shows the calculated effect of this behaviour on affected birth prevalence in relation to average final family size. (Population total fertility rate (TFR) is used as a proxy for final family size.)



Figure 8. Maximum possible effect of retrospective genetic counselling on the birth prevalence of a severe recessive disorder (a) in the absence of any risk information (red); (b) if parents limit their family after 2 unaffected children (blue), (b) if parents stop after 1 affected child (yellow), (c) if they stop completely after diagnosis of the first affected, or use prenatal diagnosis to avoid further affected births (black). For details of the calculation see *Article 9. Haemoglobin disorders epidemiology*.

The MGDb calculates potential maximum effect in relation to local total fertility rate (TFR).[[22]](#footnote-22) The figure shows that when this is 2.5 or less (as is increasingly the case) retrospective risk detection has relatively little effect on affected birth prevalence. Retrospective risk identification is potentially far more powerful in populations where parental consanguinity is common because in this situation extended family studies may identify other at-risk couples prospectively.

### Prospective risk detection

Haemoglobin disorders are typical recessive single gene disorders distinguished only by the fact that they are common, carriers can be identified prospectively by simple blood tests, and informed carrier couples often take steps to minimise their risk. Therefore, population screening and genetic counselling are cost-effective and widely practised. Since good surveillance data exist, the haemoglobin disorders now provide a model for predicting the potential future effect of DNA-based carrier detection for the full range of rare single gene disorders.

Figure 9 shows how prospective detection and genetic counselling for reproductive risk of severe single gene disorders could transform outcomes at the public health level. For details of the calculation see *Article 9. Haemoglobin disorders: epidemiology*.



Figure 9. Theoretical calculation of the maximum possible effect of *prospective* genetic risk detection and counselling on birth prevalence of severe recessive disorders. The statistical effect depends on the population average for final family size. If all detected at risk couples decided to separate, or remain childless, or use prenatal diagnosis and termination of pregnancy to ensure a disease-free family, affected birth prevalence could fall to near zero. When the option of termination of pregnancy is not available informed couples tend to limit final family size once they have one or two unaffected children. The middle curves show the maximum possible effects of such behaviour. There may be a marked effect when average final family size is large, but when it is less than 3 prospective risk detection has relatively little effect on affected birth prevalence.

## Termination of pregnancy for fetal impairment

EUROCAT and ICBDSR report rates for termination of pregnancy by country, year and disorder group.

Table 8 shows the evolution of termination of pregnancy in Western Europe disorder group, based on EUROCAT data. Rates rose rapidly from 1980 to 2012: Current EUROCAT data indicate that they have since remained relatively stable . Rates are very high for severe incurable disorders, but much lower for curable congenital malformations.

Where termination of pregnancy for fetal impairment is not legal most pregnancies that would otherwise be terminated end in fetal death, under-5 death or life-long disability.

Table 8. Evolution of termination of pregnancy for chromosomal disorders and isolated congenital malformations, based on EUROCAT 2015 data.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Main group | Disorder group | 1980-84 | 1985-89 | 1990-94 | 1995-99 | 2000-04 | **2005-09** | 2010-12 |
| Congenital malformations | Anencephaly | 32.9 | 61.2 | 81.5 | 82.5 | 87.0 | **91.5** | 85.0 |
| Spina bif & e'cele | 8.2 | 21.3 | 33.6 | 50.5 | 59.7 | **67.4** | 48.1 |
| Oro-facial clefts | 0.8 | 1.8 | 1.7 | 1.8 | 2.0 | **2.9** | 2.9 |
| Congen heart disease | 0.5 | 2.4 | 3.7 | 4.1 | 4.3 | **4.4** | 5.4 |
| Severe other malfns | 1.6 | 6.0 | 8.7 | 10.6 | 11.3 | **11.0** | 10.1 |
| Less severe malfns | 0.2 | 1.6 | 3.2 | 3.6 | 3.6 | **3.6** | 3.0 |
| Chromosomal disorders | Down syndrome | 4.3 | 14.7 | 28.3 | 45.2 | 52.9 | **58.7** | 61.4 |
| Other trisomies | 8.2 | 39.8 | 57.1 | 67.7 | 75.7 | **81.4** | 82.9 |
| Rare chromosomal | 9.3 | 23.7 | 54.6 | 47.8 | 41.7 | **42.1** | 50.4 |
| Turner syndrome | 32.9 | 45.1 | 58.2 | 64.9 | 65.7 | **69.9** | 72.6 |

The rates published by EUROCAT and ICBDSR represent the choices of informed at-risk parents and so may be used as a guide for termination of pregnancy rates elsewhere, in the context of access to services and reported legality of termination of pregnancy for fetal impairment. Table 9 shows the resulting global estimates. However, the estimates must be viewed as strictly provisional because of the very limited availability of relevant information.

Table 9. Estimates of the proportion of affected pregnancies terminated in 2020-24 by disorder group and WHO region.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| WHO region | Down syndrome | Other autosomal | Sex chromo-somal | Severe congen malfns | Less severe malfns | Rare single gene | Hb dis-orders | Total % TOP |
| AFR | 0.23 | 0.55 | 0.13 | 0.10 | 0.03 | 0.14 | 0.27 | 0.2 |
| AMR | 8.99 | 9.69 | 2.20 | 1.29 | 0.54 | 2.03 | 7.96 | 2.3 |
| EMR | 1.57 | 3.42 | 0.72 | 0.67 | 0.18 | 0.40 | 7.33 | 0.8 |
| EUR | 36.49 | 49.90 | 10.02 | 8.68 | 2.54 | 3.52 | 47.40 | 10.5 |
| SEAR | 2.48 | 5.62 | 1.30 | 2.00 | 0.33 | 0.94 | 12.74 | 2.0 |
| WPR | 24.92 | 47.79 | 10.56 | 12.41 | 2.64 | 3.15 | 37.94 | 11.7 |
| World | 8.63 | 13.69 | 2.88 | 3.17 | 0.72 | 0.92 | 2.81 | 2.8 |
| W Europe | 57.03 | 64.79 | 13.23 | 9.11 | 3.20 | 4.12 | 41.25 | 14.7 |

## Early diagnosis and care

The ultimate objective of patient care is to enable a normal length and quality of life. This can be fully achieved for neonatal jaundice and the approximately 70% of congenital malformations that can be corrected by paediatric surgery but is only partially feasible for incurable disorders. In such cases reduction in early mortality leads to a cumulative increase in numbers surviving with disability and long-term service needs. The progressive increase is particularly marked for single gene disorders.

## Summary

Table 8 shows that globally, current interventions may have reduced adverse outcomes of endogenous congenital disorders by around 20%. Table 9 shows that the maximum reduction with full implementation of interventions would be around 55%. Tables 10 and 11 compare estimated actual reduction in adverse outcomes due to interventions in 2020-24, with the potential reduction if all interventions were fully implemented by type of intervention.

Table 10. Endogenous congenital disorders. Estimated actual reduction in adverse outcomes 2020-24, by type of intervention and WHO.

|  |  |  |  |
| --- | --- | --- | --- |
| WHO region | WPP births 1,000s | Total baseline births /1,000 | Actual reduction due to interventions |
| Rates /1,000 births | Actual % reduction |
| Folic acid | Genet. couns. | Anti-D | TOP | Cure | Total reduction 2020-24 |
| EMR | 16,906 | 52.0 | 0.66 | 0.22 | 1.51 | 0.82 | 4.44 | 7.0 | 15 |
| AFR | 34,647 | 46.3 | 0.33 | 0.14 | 0.84 | 0.16 | 1.15 | 2.3 | 5 |
| SEAR | 37,304 | 37.8 | 0.01 | 0.04 | 0.43 | 0.76 | 2.73 | 4.0 | 11 |
| EUR | 11,296 | 35.8 | 0.18 | 0.04 | 2.54 | 3.93 | 12.44 | 19.0 | 53 |
| AMR | 15,319 | 34.5 | 0.98 | 0.01 | 2.20 | 1.27 | 8.95 | 12.4 | 36 |
| WPR | 24,368 | 31.4 | 0.01 | 0.06 | 0.17 | 3.90 | 11.31 | 15.5 | 49 |
| World | 139,840 | 40.0 | 0.29 | 0.09 | 0.98 | 1.48 | 5.53 | 8.1 | 20 |
|  W Europe | 4,424 | 34.9 | 0.00 | 0.06 | 2.87 | 5.06 | 14.28 | 22.3 | 64 |

Table 11. Endogenous congenital disorders. Potential reduction in adverse outcomes if all interventions were fully implemented, by type of intervention and WHO region.

|  |  |  |  |
| --- | --- | --- | --- |
| WHO region | WPP births 1,000s | Total baseline births /1,000 | Potential reduction if all interventions implemented |
| Rates /1,000 births | Potential % reduction |
| Folic acid | Genet. couns. | Anti-D | TOP | Cure | Total actual reduction /1,000 |
| EMR | 16,906 | 52.0 | 2.11 | 0.84 | 3.72 | 4.84 | 14.10 | 25.6 | 49 |
| AFR | 34,647 | 46.3 | 0.58 | 1.71 | 2.94 | 4.43 | 12.73 | 22.4 | 48 |
| SEAR | 37,304 | 37.8 | 2.34 | 0.63 | 1.40 | 4.16 | 13.65 | 22.2 | 59 |
| EUR | 11,296 | 35.8 | 0.65 | 0.13 | 2.72 | 4.42 | 13.83 | 21.8 | 61 |
| AMR | 15,319 | 34.5 | 0.67 | 0.13 | 2.79 | 4.26 | 13.96 | 21.8 | 63 |
| WPR | 24,368 | 31.4 | 1.26 | 0.35 | 0.20 | 4.14 | 13.32 | 19.3 | 61 |
| World | 139,840 | 40.0 | 1.37 | 0.78 | 2.11 | 4.34 | 13.47 | 22.1 | 55 |
|  W Europe | 4,424 | 34.9 | 0.11 | 0.12 | 2.87 | 4.66 | 14.30 | 22.1 | 64 |

# Discussion

## Reliability of the estimates

Baseline birth prevalence is the most important estimate because it defines the total envelope for each disorder group. Table 12 shows factors affecting the reliability of the MGDb estimates. There is good reason to consider that the baseline birth prevalences of chromosomal and consanguinity-associated disorders are reliable; some under-estimation is likely for congenital malformations and rare single gene disorders; some over-estimation is likely for haemoglobin disorders because carrier prevalence falls as malaria comes under control. Estimates for the two genetic risk factors are very approximate.

Table 12. Factors affecting the reliability of MGDb estimates of baseline birth prevalence of endogenous congenital disorders

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Disorder group | Based on | Details | Reliability | Comment |
| Chromosomal disorders | Maternal age relationship, observational data | Equation based on maternal age distribution: umbrella registries | High |  |
| Congenital malformations | EUROCAT congenital anomaly registries | EUROCAT 30 yr averages (2000-09) updated 2015. | High | Definitely some under-estimation |
| Rare single gene disorders | British Columbia Health Surveillance Registry (Baird et al. 1988), other literature | Similar rate worldwide (basic population genetics: Bodmer & Cavalli-Sforza 1976, etc)  | Moderate | Probably some under-estimation |
| Consanguinity-associated disorders | Prospective study (UK) (Bundey & Alam 1993). Attributable early mortality (Bittles and Black 2010a&b) | Equation based on population coefficient of consanguinity | High | Good estimates of fetal death and early mortality due to recessive disorders |
| Haemoglobin disorders | Database of population-specific carrier prevalences | Livingstone 1985, Modell & Darlison 2008 updated | Moderate | Uncertainty: falling carrier prevalence with malaria control. |
| Rhesus haemolytic disease | Database of population-specific carrier prevalences | Mourant 1976, Bhutani et al. 2013. | Moderate | Uncertainty: rates for maternal immunisation & livebirth outcomes based on North European populations. |
| G6PD deficiency neonatal jaundice | Database of population-specific carrier prevalences | Livingstone 1985, Howes et al. 2012 | Low | Only risk can be reliably calculated because of major role of environmental factors |

There is more uncertainty about MGDb outcome estimates. These are based on two relatively clear end-points - observed outcomes with 100% access to services and outcomes with no care, but country outcomes are calculated on the basis of estimated access to services and this has many limitations. There is also considerable evidence of under-ascertainment of fetal death/stillbirth in the sources used. Data are available for survival with 100% access to care at least age 20 for most disorder groups, but reports on long-term survival are more limited. Limited observational data are available on survival in the absence of care.

Thus, there is a hierarchy of uncertainty in the MGDb estimates.

* Baseline birth prevalence estimates are evidence-based and may be used with reasonable confidence as a starting point for country-specific outcome estimates.
* Outcome estimates with no care and 100% access to services are susceptible to change and require regular review.
* Country-specific estimates need stringent critical review by local experts.

## Provisional estimates for environmental disorders

Until recently, the main focus of policy-makers in lower income settings has been on environmental congenital disorders. Interventions such as iodization of salt, immunization against rubella, diagnosis and treatment of maternal infection, and avoidance of environmental risks have reduced the birth prevalence of most environmental congenital disorders to a very low level in high income countries, but they remain common in many low- and middle-income countries. It is however difficult to estimate their past and present prevalence in these countries because of the limited availability of surveillance data.

Prevention of congenital disorders converts early death or life-long disability to an unaffected life and so ranks among the most effective of health interventions. It is therefore desirable to attempt some estimate, however approximate, of their population effect.

Estimates could be attempted for five common congenital infections using global assessments available in the literature: rubella (Cutts et al. 1997), syphilis (Newman et al. 2013), cytomegalovirus (Lanzieri et al. 2014), toxoplasmosis (Moncada et al. 2012) and HIV/AIDS (Global Burden of Disease study, GBD). Table 13 summarises the resulting estimate of their global impact in 2010-14.

Table 13. Provisional estimate of the effect of interventions for prevention of congenital infections in 2020-24

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| WHO Region | WPP Av ann births 1,000s | Congenital infections /1,000 births | % reduct-ion | Annual numbers |
| Total adverse outcomes no care | Actual total adverse outcomes | Difference | Total adverse outcomes if no care | Actual total adverse outcomes | Annual gain in unaffected births |
| AFR | 34,647 | 12.6 | 5.7 | 6.9 | 55 | 437,234 | 196,730 | 240,503 |
| AMR | 15,319 | 4.1 | 1.4 | 2.7 | 65 | 62,448 | 21,771 | 40,677 |
| EMR | 16,906 | 3.3 | 2.3 | 1.0 | 31 | 56,521 | 38,999 | 17,522 |
| EUR | 11,296 | 2.3 | 0.9 | 1.4 | 60 | 26,001 | 10,286 | 15,714 |
| SEAR | 37,304 | 9.4 | 3.2 | 6.1 | 65 | 349,232 | 121,082 | 228,150 |
| WPR | 24,368 | 3.1 | 1.2 | 1.9 | 60 | 75,559 | 29,847 | 45,711 |
| World | 139,840 | 7.2 | 3.0 | 4.2 | 58 | 1,006,994 | 418,716 | 588,278 |
| W Europe | 4,424 | 1.9 | 0.7 | 1.2 | 62 | 8,438 | 3,185 | 5,253 |

It is reasonable to assume that other preventive interventions have an at least equivalent impact. If so, it is possible to make a provisional order-of magnitude *minimum* estimate by doubling the estimates in Table 12.

Table 14 compares these provisional estimates of the present birth prevalence of environmental disorders with MGDb estimates for endogenous disorders. It suggests that environmental disorders may currently account for around 26% of total global under-5 deaths attributable to congenital disorders, ranging from 35% in Africa to around 10% in Western Europe.

Table 14. Comparison of estimated baseline birth prevalence rates, and relative contributions of environmental and endogenous congenital disorders to total congenital disorders, by WHO region. (Estimates for 2010-14)

|  |  |  |  |
| --- | --- | --- | --- |
| **WHO Region** | WPP Av ann births 1,000s | Rate /1,000 births | Environmental, % of total congenital disorders |
| "Baseline" congenital infections  | Est. total environ-mental disorders | Baseline endogenous congenital disorders | Total "baseline" congenital disorders |
| AFR | 34,647 | 12.6 | 25.2 | **46.3** | 71.5 | 35 |
| AMR | 15,319 | 4.1 | 8.2 | **34.5** | 42.7 | 19 |
| EMR | 16,906 | 3.3 | 6.7 | **52** | 58.7 | 11 |
| EUR | 11,296 | 2.3 | 4.6 | **35.8** | 40.4 | 11 |
| SEAR | 37,304 | 9.4 | 18.7 | **37.8** | 56.5 | 33 |
| WPR | 24,368 | 3.1 | 6.2 | **31.4** | 37.6 | 16 |
| World | 139,840 | 7.2 | 14.4 | **40** | 54.4 | 26 |
| W Europe | 4,424 | 1.9 | 3.8 | **34.9** | 38.7 | 10 |

## Comparison with other estimates

### The March of Dimes (MOD) report (Christianson et al. 2006)

The estimates of birth prevalence and outcomes in the March of Dimes report were based on the studies of Czeizel and Sankananarayanan (1984) and Baird et al (1988) together with available disorder-specific reports. The positive reception of the MOD report (WHO 2006) encouraged further development of the MGDb.

Since 2015 the MGDb has used the ongoing EUROCAT estimates of baseline birth prevalence and birth outcomes. The EUROCAT rates include only defects that usually lead to death or disability in the absence of intervention and so are lower than MOD rates for some disorder groups, but there is generally good correspondence when the appropriate adjustments are made. There is however an exception. EUROCAT estimates 7.1/1,000 for congenital heart *defects*, but many defects never cause a health problem. To allow for this the MGDb uses a rate of 3.3/1,000 for congenital heart *disease* (See Article 7.3 Congenital heart disease).

### The global Burden of Disease (GBD) study

The GBD publishes country-specific estimates of incidence mortality and disability for a wide range of diseases at (<https://vizhub.healthdata.org/gbd-results/>. However, the GBD heading “Congenital birth defects” only covers congenital anomalies (chromosomal disorders and congenital malformations). Haemoglobin disorders and G6PD deficiency are included elsewhere but there are no collective GBD estimates for rare single gene disorders.

The 2019 GBD distinguishes 10 groups of congenital birth defects (Down syndrome, Turner and Klinefelter syndromes, other chromosomal disorders, neural tube defects, oro-facial clefts, congenital heart defects, musculo-skeletal, urogenital and other congenital malformations) and publishes estimates for “incidence” (live birth prevalence) and mortality and disability in terms of annual numbers and rates per 100,000 population. Table 15 compares MGDb and GBD estimates of under-5 mortality due to total congenital anomalies.

Table 15. Comparison of MGDb and GBD estimates of under-5 deaths due to congenital anomalies, ranked in ascending order of GBD proportion of MGDb

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| WHO region | WPP U-5 MR 2021 | Under-5 deaths /1,000 births | % of WPP under-5 deaths | GBD propn of MGDb |
| MGDb 2020-24 | GBD 2019 | MGDb | GBD |
| SEAR | 29.1 | 8.50 | 2.82 | 29.2 | 7.9 | 0.27 |
| AFR | 70.1 | 10.31 | 4.94 | 14.7 | 6.5 | 0.44 |
| EMR | 45.2 | 8.54 | 4.36 | 18.9 | 8.9 | 0.47 |
| WPR | 11.5 | 2.35 | 1.92 | 20.4 | 13.9 | 0.68 |
| EUR | 7.3 | 1.17 | 1.81 | 15.9 | 19.6 | 1.23 |
| AMR | 13.2 | 2.04 | 3.20 | 15.4 | 20.7 | 1.34 |
| World | 37.8 | 6.99 | 3.38 | 18.5 | 8.5 | 0.46 |
| W Europe | 3.6 | 0.67 | 0.96 | 18.7 | 27.2 | 1.46 |

At the global level GBD estimates are only half those of the MGDb, but they are higher than MGDb estimates for higher income regions and much lower for lower income regions. The implications of this difference are discussed in Article 16, Comparison of MGDb and GBD estimates.

Another reason for concern is that though the GBD mortality estimates only apply for *congenital anomalies* they are widely understood to cover all *congenital disorders*. Table 16 shows the MGDb 2020-24 estimate of additional under-5 deaths due to single gene disorders. There are large regional differences due to the uneven distribution of haemoglobin disorders and parental consanguinity, but the global estimate of 6.8/1,000 is close to the 7/1,000 estimate for total congenital anomalies. Even if there is some over-estimation in the MGDb estimates it is clear that single gene disorders make a major but overlooked contribution to early mortality due to congenital disorders.

Table 16. MGDb estimates of the contribution of congenital anomalies and single gene disorders to total under-5 mortality (2020-24)

|  |  |  |  |
| --- | --- | --- | --- |
| WHO region | WPP Under-5 deaths /1,000 | Under-5 deaths /1,000 | Proportion of total under-5 deaths |
| Total congen anomalies | Total single gene  | Total CA & single gene | Total congen anomalies | Total single gene  | Total CA & single gene |
| AFR  | 70.1 | 10.31 | 11.04 | 21.4 | 14.7 | 15.8 | 30.5 |
| AMR  | 13.2 | 2.04 | 2.03 | 4.1 | 15.4 | 15.4 | 30.8 |
| EMR  | 45.2 | 8.54 | 11.51 | 20.1 | 18.9 | 25.5 | 44.4 |
| EUR  | 7.3 | 1.17 | 2.43 | 3.6 | 15.9 | 33.1 | 49.0 |
| SEAR  | 29.1 | 8.50 | 5.09 | 13.6 | 29.2 | 17.5 | 46.7 |
| WPR  | 11.5 | 2.35 | 2.13 | 4.5 | 20.4 | 18.5 | 38.8 |
| World | 37.8 | 6.99 | 6.83 | 13.8 | 18.5 | 18.1 | 36.6 |
| W Europe  | 3.6 | 0.67 | 1.70 | 2.4 | 18.7 | 47.3 | 65.9 |

### Need for an agreed terminology for congenital disorders

The contrast between the MGDb and GBD estimates underlines the need for a consensus on the terminology used for congenital disorders. Figure 10 shows the bundling of congenital disorder groups used for different purposes. All the groups in the figure fall within the WHO definition of congenital disorders, but groups overlap and different professionals count and bundle the disorders in different ways. Clear definitions are essential to avoid misunderstanding.



Figure 10. Bundling of the main groups of congenital disorder used for different professional purposes. The chart shows the distinction used here between environmental and endogenous disorders. The ICD10 definition of congenital anomalies includes only disorders with structural effects and so excludes many environmental and most genetic disorders. Genetic disorders include chromosomal disorders but exclude environmental disorders and most congenital malformations. Only congenital infections fall within the WHO definition of communicable diseases, all the rest are non-communicable. The rare diseases grouping (e.g. globalgenes.org) includes some disorders in all groups.

The definitions used in the MGDb are collated in Article *1.1 Terminology* in the hope of promoting a consensus on terms suitable for use in Community Genetics.

# Conclusion

The MGDb estimates of birth prevalence and outcomes of early-onset congenital disorders have many limitations, but they are useful indicators of health burden in settings with only limited or unreliable observational data. They offer a starting point for service planning for care, prevention and surveillance of these disorders.

# References

1. Alwan AA, Modell B. Community Control of Genetic and Congenital Disorders. EMRO Technical Publications Series 24. World Health Organisation Regional Office for the Eastern Mediterranean. 1997. (218 pp) ISBN 92-9021-220-9. ISSN 1020-0428.
2. Arth A, Kancherla V, Pachon H, Zimmerman S, Johnson Q, Oakley GP. A 2015 Global Update on Folic Acid-Preventable Spina Bifida and Anencephaly. Birth Defects Res A Clin Mol Teratol. 2016 Jul;106(7):520-9. doi: 10.1002/bdra.23529. (Published online 15 July 2016 in Wiley Online Library (wileyonlinelibrary.com).
3. Ash P, Vennart J, Carter CO. 1977. The incidence of hereditary disease in man. Lancet. 1(8016):849-51.
4. Baird PA, Anderson TW, Newcombe HB, Lowry RB. 1988. Genetic disorders in children and young adults: a population study. American Journal of Human Genetics 42: 677-693.
5. Baird PA. 1987. Measuring birth defects and handicapping disorders in the population: the British Columbia Health Surveillance Registry. Canadian Medical Association Journal 136: 109-111.
6. Baird PA, Anderson TW, Newcombe HB, Lowry RB. 1988. Genetic disorders in children and young adults: a population study. American Journal of Human Genetics 42: 677-693.
7. Bhutani VK, Zipursky , Blencowe et al. 2013. Beyond newborn survival paper 6. Neonatal hyperbilirubinaemia and Rhesus disease of the newborn: incidence and impairment estimates for 2010 at regional and global levels. Pediatric Research 74: 86-100.
8. Bittles AH. [www.consang.net](http://www.consang.net).
9. Bittles AH & Black ML (2010a) The impact of consanguinity on neonatal and infant health. *Early human development* **86**(11)**,** 737-741.
10. Bittles AH & Black ML (2010b) Consanguinity, human evolution, and complex diseases. *Proceedings of the National Academy of Sciences* **107**(suppl\_1)**,** 1779-1786.
11. Bodmer WF & Cavalli-Sforza LL (1976) *Genetics, evolution, and man*. WH Freeman & Co Ltd.
12. Bundey S & Alam H (1993) A five-year prospective study of the health of children in different ethnic groups, with particular reference to the effect of inbreeding. *European Journal of Human Genetics* **1**(3)**,** 206-219.
13. Carter CO. Monogenic disorders. 1977. Journal of Medical Genetics 14: 316-320.
14. Christianson A, Howson C, Modell B. 2006. March of Dimes Global Report on Birth Defects. The hidden toll of dying and disabled children. March of Dimes Birth Defects Foundation, White Plains, New York. 2006. http://www.marchofdimes.com/professionals/871\_18587.asp.
15. Christianson A, Modell B. Medical genetics in developing countries. Annual Review of Genetics and Human Genomics. 2004. 5. 219-265.
16. Clarke C. 1983. Prevention of Rh haemolytic disease by immunoglobulin anti-D. Vox Sanguinis 44: 396-399.
17. Cutts FT, Robertson SE, Diaz-Ortega J-L, Samuel R. 1997. Control of rubella and congenital rubella syndrome (CRS) in developing countries, part 1: burden of disease from CRS. Bulletin of the World Health Organization, 1997, 75 (1): 55-68.
18. Czeizel A, Dobó M, Dudás I, Gasztonyi Z, Lantos I. 1998. The Hungarian periconceptional service as a model for community genetics. Community Genet. 1998;1(4):252-9.
19. Czeizel AE & Dudas I (1992) Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *New England Journal of Medicine* **327**(26)**,** 1832-1835.
20. Czeizel A, Intody Z, Modell B. 1993. What proportion of congenital anomalies can be prevented? British Medical Journal 306: 499-502.
21. Czeizel A, Sankaranarayanan K. 1984. The load of genetic and partly genetic disorders in man. 1. Congenital anomalies: estimates of detriment in terms of years of life lost and years of impaired life. Mutation Research 128: 73 - 103.
22. Czeizel A. 1989. The Hungarian surveillance of new mutations: lack of detectable increase in the occurrence of indicator conditions caused by germinal mutations in Hungary following Chernobyl nuclear power plant accident. Human Genetics 82:359-66.1989.
23. Czeizel A. 1992. Prevention of first occurrence of neural tube defects. Results of the Hungarian randomised controlled trial of periconceptional vitamin supplementation. New England Journal of Medicine 327: 1832-5.
24. Czeizel AE, Dobó M, Dudás I, Gasztonyi Z, Lantos I. 1998. The Hungarian periconceptional service as a model for community genetics. Community Genet. 1998;1(4):252-9.
25. Czeizel AE, Toth M, Rockenbauer M. 1996. Population-based case control study of folic acid supplementation during pregnancy. Teratology 53: 345-51.
26. Czeizel AE. 1993. Prevention of congenital abnormalities by periconceptional multivitamin supplementation. British Medical Journal 306: 1645-8.
27. Czeizel AE. 1997. First 25 years of the Hungarian congenital abnormality registry. Teratology 55(5):299-305.
28. Czeizel AE. 2012. Experience of the Hungarian Preconception Service between 1984 and 2010. Eur J Obstet Gynecol Reprod Biol. 2012 Mar;161(1):18-25. doi: 10.1016/j.ejogrb.2011.12.019. Epub 2012 Jan 18.
29. Global Burden of Disease (GBD) study 2019 (https://vizhub.healthdata.org).
30. Hook EB, Hamerton JL. 1977. The frequency of chromosome abnormalities detected in consecutive newborn studies – differences between studies – results by sex and by severity of phenotypic involvement. In Hook EB and Porter JH eds. Population cytogenetics. Academic Press. New York. 1977.
31. Howes RE, Piel FB, Patil AP *et al.* (2012) G6PD deficiency prevalence and estimates of affected populations in malaria endemic countries: a geostatistical model-based map. *PLoS medicine* **9**(11)**,** e1001339.
32. Kancherla V, Wagh K, Johnson Q, Oakley GP. 2018. A 2017 global update on folic acid-preventable spina bifida and anencephaly. Birth Defects Research. 2018; 1–9. <https://doi.org/10.1002/bdr2.1366>
33. Lanzieri TM, Dollard SC, Bialek SR, Grosse S. 2014. Systematic review of the birth prevalence of congenital cytomegalovirus infection in developing countries. International Journal of Infectious Diseases 22: 44-48.
34. Livingstone FB . Frequencies of Hemoglobin Variants. Thalassemia, G6PD variants and ovalocytosis in human populations. Oxford University Press, New York and Oxford 1985.
35. Luzzatto L, Mehta A. Glucose-6-phosphate dehydrogenase deficiency. In Scriver CR, Beaudet AL, Sly WS, Valle D. (Eds). The metabolic basis of inherited disease. 7th edition. McGraw Hill Inc, New York. 1995.
36. Malherbe HL, Modell B, Blencowe H, Strong KL, Aldous C. A review of key terminology and definitions used for birth defects globally. J Community Genet. 2023;14:241-62. https//www.doi.org/10.1007/s12687-023-00642-2.
37. Modell B, Darlison M. 2008. Global epidemiology of haemoglobin disorders, and derived service indicators. Bulletin of the WHO 86. 480-7.
38. Modell B, Kuliev AM, Wagner M. Community Genetics Services in Europe. WHO Regional Publications, European Series No 38. WHO Regional Office for Europe, 8 Scherfigsvej, DK-2100, Copenhagen, Denmark. 1992. ISBN 92 890 1301 X. ISSN 0378-2255.
39. Moncada PA, Montoya JG. Toxoplasmosis in the fetus and newborn: an update on prevalence, diagnosis and treatment. Expert Rev. Anti Infect. Ther. 10(7), 815–828 (2012).
40. Mourant AE, Kopec AC, Domaniewska-Sobczak. The distribution of the human blood groups and other polymorphisms. Oxford university Press 1976.
41. Murdock GP (1967) Ethnographic atlas: a summary. *Ethnology* **6**(2)**,** 109-236.
42. Myrianthopoulos NC, Chung CS. 1974. Congenital malformations in singletons: epidemiological survey. Birth Defects Original Articles Series Vol 10. 1-58. The National Foundation March of Dimes.
43. Nacul LC, Stewart A, Alberg C, Chowdhury S, Darlison MW, Grollman C. Hall A, Modell B, Moorthie S, Sagoo GS, Burton H. 2013. A Toolkit to assess health needs for congenital disorders in low- and middle-income countries: an instrument for public health action. Journal of Public Health 36: 243-250.
44. Neel JV. 1958. A study of major congenital defects in Japanese infants. American Journal of Human Genetics 10: 398-445.
45. Newman L, Kamb M, Hawkes S, Gomez G, SayL, Seuc A, Broutet N. 2013. Global Estimates of Syphilis in Pregnancy and Associated Adverse Outcomes: Analysis of Multinational Antenatal Surveillance Data. PLOS medicine February 2013 | Volume 10 | Issue 2 | e1001396.
46. Schull WJ, Neel JV. The effects of inbreeding on Japanese children. Harper and Row, New York. 1956.
47. Schull WJ. 1958. Empirical risks in consanguineous marriages: sex ratio, malformation and viability. American Journal of Human Genetics 10: 294-343.
48. Schull WJ. 2003. The children of atomic bomb survivors: a synopsis. J. Radiol. Prot. 23: 369–384. 2003.
49. Schull WJ, Otake M, Neel JV (1981) Genetic effects of the atomic bombs: a reappraisal. Science 213:1220-1227.
50. Stevens GA et al. 2016. Guidelines for accurate and transparent health estimates reporting: the GATHER statement. PLOS Medicine June 28 2016.
51. Stevenson AC 1959. The load of hereditary defects in human populations. Radiation Research, Supplement 1: 306-325.
52. Tennant PW, Pearce MS, Bythell M *et al.* (2010) 20-year survival of children born with congenital anomalies: a population-based study. *The Lancet* **375**(9715)**,** 649-656.
53. Trimble BK, Doughty JH. 1974. The amount of hereditary disease in human populations. Annals of Human Genetics 38: 199-223.
54. United Nations Scientific Committee on the Effects of Atomic Radiation. 1977. Sources and biological effects of ionising radiation. 1977 report to the General Assembly, with Annexes. United Nations Publications. Sales number E.77.IX.I. New York.
55. United Nations Scientific Committee on the Effects of Atomic Radiation. 1982. Sources and biological effects. 1982 report to the General Assembly, with Annexes. United Nations Publications. Sales number E.82.IX.06300P. New York.
56. United Nations Scientific Committee on the Effects of Atomic Radiation. 1986. Genetic and somatic effect of ionising radiation. United Nations, New York.
57. WHO 1966a. Congenital malformations. A report of a study of a series of consecutive births in 24 centres. Stevenson AC, Johnston HA, Stewart MIP, Golding DR. WHO technical report. Geneva.
58. WHO 1966b. Haemoglobinopathies and allied disorders. Report of a WHO scientific group. World Health Organization Technical Report Series 1966, No 338. Geneva.
59. WHO 1972. Treatment of haemoglobinopathies and allied disorders. Report of a WHO scientific Group. World Health Organization Technical Report Series 1972, No 509. Geneva.
60. WHO 1982. WHO Working Group. Hereditary Anaemias: genetic basis, clinical features, diagnosis and treatment. Bulletin of the World Health Organisation 60: 643-660. 1982.
61. WHO 1983. Memorandum from a WHO meeting. Community Control of Hereditary Anaemias, Bulletin of the World Health Organisation 61: 63-80. 1983.
62. WHO 1985a. Community approaches to the control of hereditary diseases. Report of a WHO Advisory Group on Hereditary Diseases. Geneva 3‑5 October 1985. Unpublished WHO document HMG/AG/85.10. http://www.who.int/genomics/publications/en/index.html
63. WHO 1985b. Update of the Progress of Haemoglobinopathies Control. Report of the Third and Fourth Annual Meetings of the WHO Working Group for the Community Control of Hereditary Anaemias. Unpublished Report of the WHO: HMG/WG/85.8.
64. WHO 2000. Primary health care approaches for the control of congenital disorders and disability. Report of a WHO meeting Cairo, 6-8 December 1999. WHO/HGN/WG/00.1
65. WHO 2004. de Benoist B, Andersson M, Egli I, Takkouche B, Allen H. Iodine status worldwide. WHO MGDb on Iodine Deficiency.
66. WHO 2006. Management of birth defects & haemoglobin disorders. Report of a joint WHO-MOD meeting. WHO, Geneva, Switzerland. May, 2006.
67. WHO 2013a. Meeting to develop a global consensus on preconception care to reduce maternal and childhood mortality and morbidity. Geneva, World Health Organization, 2013.
68. WHO 2013b. Policy brief: Preconception care: maximising the benefits for maternal and child health. <http://www.who.int/maternal_child_adolescent/documents/preconception_care_policy_brief.pdf>
69. Williams EJ, Embleton ND, Clark JE, Bythell M, Ward Platt MP, Berrington JE. 2013. Viral Infections: Contributions to Late Fetal Death, Stillbirth, and Infant Death. J Pediatr 2013;163:424-8. (Cytomegalovirus).
70. Williams J, Mai CT, Mulinare J, Isenburg J, Flood TJ, Ethen M, Frohnert B, Kirby. RS; Centers for Disease Control and Prevention.2015. Updated estimates of neural tube defects prevented by mandatory folic Acid fortification - United States, 1995-2011. MMWR Morb Mortal Wkly Rep. 2015 Jan 16;64(1):1-5.

# Annexes

## UNSCEAR

The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) was established by a United Nations General Assembly resolution unanimously approved in 1955, to collect and evaluate information on the levels and effects of exposure to ionizing radiation. At the time, the global arms race was escalating, and there was a high level of concern about nuclear weapons testing and its impact with regard to exposure to radiation. UNSCEAR’s first two reports to the United Nations General Assembly, in 1958 and 1962, provided an overview of human radiation exposure at that time, and laid the scientific grounds on which the Partial Test Ban Treaty on the prohibition of nuclear weapon testing in the atmosphere was negotiated and signed in 1963.The Committee recognized in its first report of 1958 that medical diagnostic and therapeutic exposures were a major component of artificial radiation exposure globally, a fact that remains true today. The Committee has continued to systematically review and evaluate global and regional levels and trends of medical exposure, as well as exposure of the public and workers. Over the decades, UNSCEAR has become the official international authority on the levels and effects of exposure to ionizing radiation resulting from natural and artificial sources. It provides policy-relevant assessments, but is not involved in deciding policy. For information only –not an official document 2. Other key activities included evaluating the evidence for radiation-induced health effects from studies of the survivors of the atomic bombings in Japan in 1945 and other exposed groups. These reviews prompted significant worldwide reductions in unnecessary radiation exposure, and continue to influence the programmes of various international bodies working in the fields of human health, nuclear energy and radiation protection. Other work included authoritative assessments of the radiological consequences of the 1986 accident at Chernobyl and, a comprehensive overview of the levels and effects of exposure following the 2011 accident at Fukushima, including a follow-up white paper. Scientists from 27 countries currently constitute the Committee, which is a subsidiary body of the General Assembly. They work on behalf of the United Nations. Many more countries and international organizations supply information for the Committee’s work. The UNSCEAR secretariat is based in Vienna, and is administered by UNEP.

## World Health Assembly 2010 resolution on Birth Defects.

World Health Assembly. 26th Session, Agenda item 4.7, 21 January 2010. (Document EB126/10).

Resolution EB126.R6. Birth defects

The Executive Board, Having considered the report on birth defects, RECOMMENDS to the Sixty-third World Health Assembly the adoption of the following resolution:

The Sixty-third World Health Assembly,

Concerned by the high number of stillbirths and neonatal deaths occurring worldwide and by the large contribution of neonatal mortality to under-five mortality;

Recognizing the importance of birth defects as a cause of stillbirths and neonatal mortality;

Mindful that effective interventions to prevent birth defects including provision of appropriate community genetic services within the primary health care are available that can be integrated into maternal, reproductive and child health services;

Concerned by the inadequate coverage of maternal, newborn and child health interventions and the barriers to access to health services that still exist in countries with the highest burden of maternal, newborn and child deaths;

Aware that the attainment of Millennium Development Goal 4 on reduction of child mortality will require accelerated progress in reducing neonatal mortality including prevention and management of birth defects;

Recalling resolution WHA58.31, in which the Health Assembly, calling for universal coverage of maternal, newborn and child health interventions, urged Member States to commit resources and to accelerate national action to build a seamless continuum of care for reproductive, maternal, newborn and child health; as well as resolution WHA57.13 which recognized that genomics has a significant contribution to make in the area of public health;

Recognizing that the prevalence of birth defects varies between communities, and that insufficient epidemiological data may hamper effective and equitable management;

Recognizing the diversity of causes and determinants of congenital disorders, including preventable factors such as infectious or nutritional factors, vaccine-preventable diseases, consumption of alcohol, tobacco and drugs, and exposure to chemical substances, notably pesticides;

Deeply concerned that birth defects are not still recognized as priorities in public health;

Concerned by the limited resources dedicated to prevention and management of birth defects in particular in middle- and low-income countries;

Welcoming the report on birth defects,

1. URGES Member States:

(1) to raise awareness among all relevant stakeholders, including government officials, health professionals, civil society and the public, about the importance of birth defects as a cause of child morbidity and mortality;

(2) to set priorities, commit resources, and develop plans and activities for integrating effective interventions that include comprehensive guidance, information and awareness raising to prevent birth defects, and care for children with birth defects into existing maternal, reproductive and child health services and social welfare for all individuals who need them;

(3) to promote the application of internationally recognized standards regulating the use of chemical substances in the air, water and soil;

(4) to increase coverage of effective prevention measures, through health education programmes that include ethical, legal and social issues associated with birth defects for the general population and high-risk groups, and by fostering the development of parent patient organizations and establishing appropriate community genetic services;

(5) to record surveillance data on birth defects as part of national health information systems;

(6) to develop expertise and to build capacity on the prevention of birth defects and care of children with birth defects;

(7) to strengthen research and studies on etiology, diagnosis and prevention of major birth defects and to promote international cooperation in combating with them;

(8) to take all necessary measures to ensure the full enjoyment by children with disabilities of all human rights and fundamental freedoms on an equal basis with other children and give priority to the child's well-being and support and facilitate families in their childcare and child-raising efforts;

(9) to raise awareness among all relevant stakeholders, including government officials, health professionals, civil society and the public, about the importance of newborn screening programmes and their role in identifying infants born with birth defects;

(10) to support families who have children with birth defects and associated disabilities, and ensure that appropriate habilitation and support is provided to children with disabilities;

2. REQUESTS the Director-General:

(1) to promote the collection of data on the global burden of mortality and morbidity due to birth defects, and to consider broadening the groups of congenital abnormalities included in the classification when the International Statistical Classification of Diseases and Related Health Problems (Tenth Revision) is revised;

(2) to continue to collaborate with the international Clearinghouse for Birth Defects Surveillance and Research in order to improve collection of data on global burden of mortality and morbidity due to birth defects;

(3) to support Member States in developing national plans for implementation of effective interventions to prevent and manage birth defects within their national maternal, newborn and child health plan, strengthening health systems and primary care, including improved vaccination coverage such as for measles and rubella, and food fortification strategies, for the prevention of birth defects, and promoting equitable access to such services;

(4) to provide support to Member States in developing the ethical and legal guidelines in relation to birth defects;

(5) to support Member States in the provision of appropriate community genetic services within the primary health-care system;

(6) to promote technical cooperation among Member States, nongovernmental organizations and other relevant bodies on prevention of birth defects;

(7) to support and facilitate research efforts on prevention and management of birth defects in order to improve the quality of life of those affected by such disorders;

(8) to report on progress in implementing this resolution to the Sixty-seventh World Health Assembly, through the Executive Board, in 2014.

Seventh meeting, 21 January 2010. EB126/SR/7

## Report of the WHO Executive Board. 126th Session EB126.R6.

Agenda item 4.7 21 January 2010. Birth defects.

The Executive Board, Having considered the report on birth defects, REQUESTS the Director-General: (1) to promote the collection of data on the global burden of mortality and morbidity due to birth defects.

Table 1. MGDb global outcome rates per 1000 live births 2020-2024 for three scenarios: no care (baseline), 100% access to care, estimated actual care (effect) including baseline birth prevalence, fetal deaths, U5 deaths, disability at age 5 in no care scenario plus pre-pregnancy reduction, TOP and effective cure for care scenarios, for early onset, endogenous congenital disorders included in the MGDb.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| World | Baseline B /1,000 | If no care | If 100% access to services | Estimated actual effect 2020-24 |
| Fetal death | U-5 death | Disabil @ 5 yr | Pre-preg redn | TOP | Fetal death | Effective cure | U-5 death | Disabil @ 5 yr | Pre-preg redn | TOP | Fetal death | Effective cure | U-5 death | Disabil @ 5 yr |
| Down syndrome | 2.11 | 14.0 | 53.7 | 32.7 | 0.0 | 56.4 | 6.1 | 0.0 | 2.3 | 33.9 | 0.0 | 8.6 | 12.8 | 0.0 | 29.0 | 48.0 |
| Other autosomal | 1.29 | 20.1 | 61.8 | 17.4 | 0.0 | 64.5 | 6.5 | 0.0 | 10.2 | 18.2 | 0.0 | 13.7 | 23.7 | 0.0 | 38.9 | 22.9 |
| Sex chromosomal | 1.12 | 6.5 | 1.1 | 88.9 | 0.0 | 14.5 | 3.5 | 0.0 | 0.7 | 78.3 | 0.0 | 2.9 | 5.9 | 0.0 | 0.9 | 86.8 |
| Severe congen malfns | 15.36 | 5.3 | 79.6 | 14.5 | 13.6 | 11.1 | 1.7 | 52.4 | 2.4 | 18.1 | 3.1 | 3.2 | 4.2 | 27.9 | 37.4 | 23.4 |
| Less severe malfns | 5.19 | 0.7 | 4.7 | 91.0 | 0.0 | 3.7 | 0.6 | 89.2 | 0.1 | 6.1 | 0.0 | 0.7 | 0.7 | 42.2 | 2.3 | 51.3 |
| Rare single gene | 10.66 | 11.0 | 58.0 | 29.6 | 3.9 | 3.5 | 10.2 | 0.0 | 26.4 | 53.4 | 1.5 | 0.9 | 10.8 | 0.0 | 46.4 | 38.8 |
| Hb disorders | 3.67 | 0.0 | 63.5 | 33.7 | 6.0 | 17.7 | 0.0 | 0.0 | 2.1 | 68.5 | 1.2 | 2.8 | 0.0 | 0.0 | 51.4 | 41.4 |
| Rh haem disease | 2.39 | 25.0 | 37.5 | 35.8 | 99.0 | 0.0 | 0.3 | 0.0 | 0.0 | 0.7 | 38.2 | 0.0 | 15.4 | 0.0 | 18.8 | 25.9 |
| G6PDd NN jaundice | 0.86 | 0.0 | 50.0 | 47.9 | 0.0 | 0.0 | 0.0 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 36.9 | 24.8 | 36.4 |
| Total MGDb | 42.6 | 7.6 | 56.9 | 34.1 | 12.0 | 12.0 | 3.8 | 31.8 | 8.1 | 30.8 | 3.7 | 2.6 | 6.7 | 15.9 | 34.0 | 35.5 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

Table 2. Bundled groups as per Table 1.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| World | Baseline B /1,000 | Fetal death | U-5 death | Disabil @ 5 yr | Pre-preg redn | TOP | Fetal death | Effective cure | U-5 death | Disabil @ 5 yr | Pre-preg redn | TOP | Fetal death | Effective cure | U-5 death | Disabil @ 5 yr |
| Total chromosomal | 4.52 | 13.9 | 42.9 | 42.3 | 0.0 | 48.3 | 5.5 | 0.0 | 4.1 | 40.5 | 0.0 | 8.6 | 14.2 | 0.0 | 24.8 | 50.5 |
| Total malformations | 20.54 | 4.1 | 60.7 | 33.8 | 10.2 | 9.2 | 1.4 | 61.7 | 1.8 | 15.1 | 2.3 | 2.5 | 3.3 | 31.5 | 28.5 | 30.4 |
| Total single gene | 14.33 | 8.2 | 59.4 | 30.7 | 4.4 | 7.2 | 7.6 | 0.0 | 20.2 | 57.3 | 1.4 | 1.4 | 8.0 | 0.0 | 47.7 | 39.5 |
| Total 2 genet risk factors | 3.26 | 18.4 | 40.8 | 39.0 | 72.8 | 0.0 | 0.2 | 26.5 | 0.0 | 0.5 | 28.1 | 0.0 | 11.4 | 9.8 | 20.4 | 28.7 |
| Total congen anomalies | 25.1 | 5.9 | 57.5 | 35.3 | 8.3 | 16.3 | 2.2 | 50.6 | 2.2 | 19.7 | 1.9 | 3.6 | 5.3 | 25.9 | 27.9 | 34.0 |
| Total congen disorders | 42.6 | 7.6 | 56.9 | 34.1 | 12.0 | 12.0 | 3.8 | 31.8 | 8.1 | 30.8 | 3.7 | 2.6 | 6.7 | 15.9 | 34.0 | 35.5 |

1. “Birth defects can be defined as structural or functional abnormalities, including metabolic disorders, which are present from birth. The term congenital disorder is considered to have the same definition; the two terms are used interchangeably.” WHO 63rd World Health Assembly. Provisional agenda item 11.7. A63/10. Birth defects. 1 April 2010. [↑](#footnote-ref-1)
2. Baseline birth prevalence i.e. prevalence in the absence of any intervention. [↑](#footnote-ref-2)
3. The methods were reviewed and approved at a meeting of international experts at the London School of Hygiene and Tropical Medicine in April 2014. The initial, now superseded method was outlined in the March of Dimes Global Report (Christianson et al. 2006). [↑](#footnote-ref-3)
4. Nevertheless, provisional very approximate modelling suggests that environmental disorders currently account for around 14% of global congenital disorders, ranging from around 20% in AFR to around 4% in Western Europe. For further consideration see Article 12 Environmental Congenital Disorders. [↑](#footnote-ref-4)
5. For example, the birth prevalence of neural tube defects is strongly influenced by maternal vitamin intake, so many cases could be classed as due to genetic risk factors. Here they are classed as endogenous because (a) no normal diet contains enough natural folate to completely prevent them and (b) there is as yet insufficient evidence to split this clearly-defined malformation group by cause. [↑](#footnote-ref-5)
6. For simplicity, in this series of articles the term “congenital disorders” is frequently used to refer to endogenous congenital disorders. [↑](#footnote-ref-6)
7. These studies covered only disorders that could be reliably detected without advanced facilities but included assessment of the effects of social class and parental consanguinity (Schull and Neel 1956, Schull 1958). [↑](#footnote-ref-7)
8. [↑](#footnote-ref-8)
9. EUROCAT definition: severe disorders = disorders that cause death or disability in the absence of intervention. [↑](#footnote-ref-9)
10. Methods were designed to comply as far as possible with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) Working Group (Stevens et al. 2016). [↑](#footnote-ref-10)
11. Usually expressed as affected per 1,000 births. [↑](#footnote-ref-11)
12. Many affected conceptions fail to implant or miscarry early in pregnancy, and do not come to the attention of health services. Such losses are extremely hard to quantify. No attempt to do so is made in MGDb. [↑](#footnote-ref-12)
13. Data from the United States is used to assess the power of folic acid food fortification, which is not current practice in most of Western Europe. [↑](#footnote-ref-13)
14. Examples include: UN .WPP). demographic data, EUROCAT and ICBDSR umbrella congenital anomaly registries, Livingstone’s database of haemoglobin disorders and G6PD deficiency, Murdock’s ethnographic atlas, Bittles’ consanguinity database, Institute for Health Metrics and Evaluation (IHME) global burden of disease (GBD) study, and key published articles e.g. Tennant et al. mortality estimates. [↑](#footnote-ref-14)
15. Note Fermi’s recommendations: not to devote more time and effort to a problem than it is worth, and not to make something more accurate than absolutely necessary. [↑](#footnote-ref-15)
16. Disorders that usually present before 20 years of age. [↑](#footnote-ref-16)
17. For a brief discussion of congenital disorders due to maternal infection see General Method Annex 2. European registry data indicate that congenital infections account for around 1% of congenital anomalies in high income settings. Obviously, the rate is far higher in lower-income settings. [↑](#footnote-ref-17)
18. Estimates based on data provided by Smile Train, an international non-governmental organisation promoting surgical repair of oro-facial clefts, are included in the Database. They show that such organisations can greatly reduce mortality and disability due to selected congenital disorders. [↑](#footnote-ref-18)
19. The power of an intervention = its quantitative effect on outcomes when fully deployed at the population level. [↑](#footnote-ref-19)
20. The method may not apply universally, e.g. there is insufficient observational data for the effect in populations of African origin with a relatively low NTD baseline birth prevalence. [↑](#footnote-ref-20)
21. If folic acid food fortification were policy in Western Europe (with the lowest baseline birth prevalence) around 20% of neural tube defects would be prevented. Most of these avoidably affected pregnancies currently end in termination of pregnancy for fetal impairment. [↑](#footnote-ref-21)
22. . [↑](#footnote-ref-22)