Supporting Documents

to the PHG Foundation Toolkit for Assessing Health Needs in relation to Congenital Disorders

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Ethical, legal and social issues

Reducing the prevalence of congenital disorders and lessening their impact potentially involves a wide range of individuals and organisations acting at many different levels. This document explores some of the ethical, legal and social issues (ELSI) which may be relevant when planning health services for populations and individuals and in developing health policies and relevant legislation[1]. After a general introduction, separate sections deal with particular issues that arise in relation to preconception, prenatal, and newborn care and screening, and longer term ELSI aspects of treatment and care of the disabled.

GENERAL BACKGROUND

Universal ethical principles

Ethical norms vary widely in different human societies and may be strongly bound up with different religious and cultural traditions. Some countries may contain many groups, each with distinct cultural and religious values. Developing health policies that are acceptable to all groups may be challenging and require extensive engagement with all stakeholders.

The philosophical tradition of the Western world may be different to that of many low and middle income countries (LMIC) and there is a possibility that the assistance it offers may assume values that many countries may not share. However, there are some ethical standards for healthcare and medical practice that are regarded as being universally applicable. These include equity, non-maleficence, beneficence, respect for persons, and confidentiality.

Equity relates to the ability of all of the population at risk to be able to benefit from a health service or intervention, and the extent to which the programme will be universally accessible. Principles such as non-maleficence and beneficence are a measure of relative harms and benefits: thus non-maleficence might focus upon the possibility of coercion, or psychological or social damage resulting from an intervention, whilst beneficence might include an assessment of how timely intervention might improve informed choices and the management or treatment of the individual or their wider family.

The principle of respect for persons may require, for example, that individuals who are offered interventions are given an opportunity to understand what is being provided and make a reasoned decision. Confidentiality entails a duty not to release personal medical information to third parties without consent, and is a cornerstone of a relationship of trust between medical professionals and patients.

Health professionals in many LMIC may struggle to maintain the highest ethical standards, especially when delivering services to large populations with very limited resources. Financial and social deprivation, or social and cultural practices, may constrain people's behaviour and ability to make autonomous choices. It is important to guard against unrealistic or culturally naive expectations with regard to ethical standards. However, it is equally important to resist the idea that they are a luxury reserved for the well-off; such attitudes may serve to perpetuate, justify and even exacerbate inequality.

One of the most pressing ethical issues relevant to policy development in many LMIC is the absence of safe and affordable medical care for many of the most vulnerable children, including those born with a congenital disorder.

Social and economic inequality

In many places, the combination of poverty and a lack of education can lead to profoundly reduced access to health services which can impact upon all stages of life. There may be wide disparities in wealth, access and opportunity; an important concern might be a lack of distributive justice if access to services and technologies is restricted to a wealthy minority[2]. Global equity and social justice may also be important in determining research priorities and the implementation of novel technologies. Wider political and economic drivers are also likely to have an impact.

Population based public health interventions: ethics and philosophy

When public health interventions are targeted at populations rather than individuals the intrusiveness and potential harms of the intervention should be balanced against the likely benefits, particularly if a degree of coercion is involved[3]. A highly intrusive intervention, or one that entails some risk to all or part of the population, will generally only be justified if it is both necessary and expected to lead to substantial benefits. Widely accessible public health education tends to be beneficial to the whole or the majority of the population but other policies that prohibit certain types of individual behaviour, such as the prohibition of smoking in confined environments, are increasingly being seen as legitimate public health policy in view of the health benefits they can confer.

Religious and cultural issues

Prevailing religious and cultural norms may influence the acceptability of services and interventions at both an individual and community level. Beliefs about the causes and risks of congenital disorders may influence the acceptability and uptake of screening and testing and the acceptability of outcomes (including timing and rationale for termination of pregnancy in the context of prenatal testing). Acceptability may also be dictated by religious traditions and rulings, which may be specific to particular countries or conditions and may change over time. For some women, giving birth to a child with a congenital disorder is regarded as a test of faith imposed by God or Allah[4]. However, there is also a need to recognise diversity within different faith groups and avoid stereotypical views based upon people's ethnicity or religion[5].

The social position and rights of women

Attitudes to women, and their legal and social rights, may profoundly influence both their own health and their prospects of giving birth to healthy children. In some countries it may be customary for women to have few rights to make decisions about their own health care, but instead defer to the wider family or social group. The role of women within society may limit access to education, treatment or services (for example, family planning and contraception), and may entail expectations about acceptable lifestyle and behaviour. At the extremes, a subservient role for women may force unwelcome choices of marriage partner or sexual behaviour.

Issues also arise when considering the respective rights of the pregnant woman and her unborn child. Respecting a woman's right to freedom of choice versus the right of her child to be born healthy is a delicate and important balance communities must strive to achieve[1].

[1] Paternal rights may also be relevant when considering the potentially detrimental impact on fetal development caused by preconception paternal exposure to dangerous substances.

Legislation and regulation

The role of regulation and legislation in safeguarding women's health, minimising the risk of congenital disorders, and ensuring optimum care for those who are born with these conditions, will vary from country to country. Measures may include, for example, occupational health laws, environmental legislation, alcohol licensing and labelling laws, regulation of healthcare provision including professional accreditation and registration for practitioners, safety and quality standards for laboratories and other testing facilities, legal rights to prenatal care, and mandatory vaccination programmes. The acceptability and feasibility of measures such as these will depend on a combination of political will and the prospects of effective enforcement, which in turn depend on affordability, social acceptability and sociocultural factors such as levels of corruption in civil institutions, the judicial system and the commercial sector.

Social rules, religious and cultural factors have a strong influence on the legal framework. In some countries there may be legal constraints on the availability of certain medications or services such as contraceptives or family planning services, or lawful access to termination of pregnancy. Legal frameworks may promote or prohibit certain types of behaviour (such as the number or spacing of children). In some situations, restrictive legislation may force people to resort to illegal practitioners to obtain medications or access to procedures such as termination of pregnancy.

Population screening

Screening has been defined as 'a process of identifying apparently healthy people who may be at increased risk of a disease or condition'[6]. Screening for diseases carries risks of stigmatisation and discrimination, even if the condition does not cause symptoms (as it might if the individual is identified as a carrier of a genetic condition) or treatment is available which renders the individual asymptomatic. The significance of this stigmatisation is that it may affect job, insurance and marriage prospects and may lead to, or be associated with, a lack of trust in medical systems and services[7].

The design and implementation of population based screening programmes raise a distinctive set of ethical issues including:

The purpose of the programme: screening must yield demonstrable clinical benefits: screening for conditions for which treatment is unavailable, or predictive testing for conditions with adult onset may raise ethical issues; the need for compatibility with local laws;

Access: the extent of public information about the programme; the need for equitable access both to the programme and to follow-up tests and treatment (including funding and reimbursement);

Informed choice and consent: the verbal and/or written information provided before and after testing (both about the screening process itself and the consequences that flow from acceptance or refusal); the process for obtaining informed consent (and/or refusal if there might be religious or other grounds for objecting to participation);

Screening process: the false positive and false negative rates of testing and the psychosocial harms that might arise as a result[8]; the disclosure of incidental findings (such as carrier status in prenatal genetic screening); and the right not to know the results;

Outcomes: ethical issues relating to privacy or confidentiality of the test itself and results generated from the test; these might include issues relating to onward communication with other family members or whether dissemination to other interested parties (such as insurers, employers, or the state) should be permitted;

On-going storage and use of samples and data: the conditions for on-going storage and provision for future use (including use for research).

Commercialisation and private providers

In many places, the only providers of some types of health services (for example, genetics services) are commercial providers, and state run services are extremely limited or non-existent (this may include where reimbursement or insurance policies exclude certain interventions or services). This has implications for access, in that only the wealthy typically have access to these services and technologies, and also for quality assurance. Tests lacking clinical validity and clinical utility may be offered by providers (on the basis that they are likely to be profitable), and services run by those who lack expertise. It may be difficult for governmental agencies to monitor the quality of services offered by commercial companies, especially if local expertise is limited.

Health economics

In order to prioritise health services effectively, there is a need for evidence of the cost-effectiveness of services and interventions. However, cost-based decisions on public funding must be balanced against considerations of equity and distributive justice or fairness[1]. Health-economic analyses often compare the costs of lifetime care of an ill or disabled person to the costs of prevention. Such calculations, while necessary to justify expenditure of limited healthcare funds may fail to adequately reflect some social and psychological 'costs' and 'benefits' that are difficult to value in monetary terms. Extreme care must also be exercised if cost-effectiveness or cost-benefit analysis is used when considering prevention of congenital disorders by termination of affected pregnancies. For example, justification of terminations on the basis of money saved may appear to devalue the lives of people who are born with these conditions, and risks accusations that prevention has a eugenic purpose.

ETHICAL, LEGAL AND SOCIAL ISSUES ARISING AT DIFFERENT STAGES OF LIFE

Preconception

Preconception interventions fall into two broad categories. Interventions may be aimed at those women who are planning or are at risk of a pregnancy and might include for example improvements in lifestyle, vaccination against infectious diseases, and food fortification or supplementation to reduce the risks to the unborn child. Other interventions are targeted at an 'at-risk' population, for example to determine their risk of recessive genetic disease (such as population based screening programmes for Tay Sach's disease in those of Jewish ancestry).

Equity of access to preconception care and interventions

Preconception care is not systematically offered in most countries. Instead, it is usually offered on an opportunistic level by primary healthcare providers or is targeted at high risk women. Barriers to equitable access to preconception care may include an already over-burdened primary healthcare system; that many pregnancies are unplanned and thus there is no opportunity for preconception care; a lack of community knowledge about the benefits of preconception care and the reproductive risks associated with specific occupations, locations or substances; organisational barriers including the lack of free health services, health insurance or ability to afford preconception care; and a lack of incentives for relevant professionals to offer preconception services. Inequity in access to preconception care may result in those with the best health having the best access to services and so widening existing inequalities.

Vaccination and/or other measures for control of infectious diseases (such as the provision of clean water, sewage disposal, refrigeration of food, and education about hygiene) can reduce the incidence of congenital disorders caused by infections such as rubella and toxoplasmosis. Many of the world's poorest people do not have access to the fundamental benefits of clean water and sanitation. In addition, vaccination is limited in many LMIC which cannot afford the vaccines or their means of delivery.

Treatment or care needs to be in place for children born with congenital disorders, regardless of whether their parents had access to, or accepted, preconception care or screening.

Consent to preventive interventions

Where possible, preconception care, including screening, should be carried out on a voluntary basis. As a general principle, coercion should not be used (which is not the case in all certain countries). Although the law recognises some instances where it is proportionate to compel an individual to undergo a particular medical test or procedure, this is usually done either to avert a public health emergency or to save a life.

Some types of preconception care may be unsolicited e.g. food fortification programmes, which may affect an entire population rather than only a specific target group. Here, the need is to strike an ethical balance between the principle of consent (which, strictly speaking, would require that food is fortified only for those who wish it) and the principle of equity (which requires that all those who might benefit from fortified food have access to it). A practical compromise might be to ensure that alternative sources of non-fortified foods are also available.

Role of and attitudes to family planning

Access to family planning is usually associated with the reduction overall in the number of children born. However, it has other important maternal and child health benefits including provision of access to nutritional supplements prior to and during pregnancy, public health information on the benefits of increased spacing between pregnancies and limiting births in women over age 35, as well as improved antenatal care for both mother and child.

Increased orofacial cleft incidence may be associated with a short interval between pregnancies: this is thought to be due to nutritional depletion, specifically folate depletion in the mother, particularly in those who are breastfeeding. Increasing the intervals between pregnancies may reduce the number of children born to women with a family history of orofacial cleft. However, achieving increased birth spacing through access to family planning methods remains challenging in many LMIC and may not be religiously or culturally acceptable in some settings. Unacceptability of or lack of access to family planning methods may also limit the usefulness of education about the risks associated with advanced maternal age which increases the risk of Down's syndrome.

Consanguinity

In some communities, marriages within an extended family group (for example, first-cousin marriages) are the norm[9]. Such marriages are often favoured because they have the social advantages of strengthening family links and mutual support, and maintaining family resources. However, extensive intermarriage within a family group can increase the risk of recessive genetic disorders[10,11]. A sensitive approach is required to ensure that at-risk individuals and couples have accurate information about their risk and any preventive measures available to them, while ensuring that families do not experience stigma and discrimination.

Preconception screening

Women who are planning or at risk of pregnancy may be screened for infectious diseases such as syphilis. In practice, this tends to occur as an adjunct to other services such as

family planning. Steps should be taken to minimise the danger that those found to be affected may suffer stigmatisation and discrimination.

Preconception screening may also be offered to detect carriers of some recessive genetic diseases. The identification of both potential parents as carriers confers a one in four risk that they will conceive an affected child. The UK Human Genetics Commission considers that those able to benefit from preconception screening should have access to it on the basis of maximising individual reproductive autonomy; and that individuals should be supported in making informed choices whenever reproductive options are available[12].

There is a risk that screening may encourage eugenic notions of a society of people without congenital disorders, relegating anyone with a congenital disorder to an underclass. Using population screening before pregnancy to determine carrier status in healthy individuals may be contentious. It is important that those who consent to screening, understand what being identified as a carrier means for their future health and that of their potential offspring. In the past, lack of understanding of conditions such as sickle cell disease and certain types of thalassaemia has led to stigmatisation and discrimination. The confidential nature of personal medical information including information about carrier status should be respected and safeguarded.

The timing of preconception genetic screening must be considered carefully. In high income countries there may be reluctance among genetics professionals to provide genetic testing to children and adolescents on the basis that their future decision-making may be compromised. However, there may be justifications for earlier genetic testing where teenage pregnancy is common or where arranged marriages are made on the basis of choices made in childhood.

If, as a result of preconception genetic screening, an individual is found to be a carrier it may be very difficult for that person's family to ask a potential partner to be tested: the preferred option is often to postpone testing until after marriage and use prenatal diagnosis to detect an affected child. This may be a particular issue for women who may be regarded as unmarriageable if found to be a carrier of a genetic condition.

Public attitudes to screening, testing and carrier screening influence their acceptability and uptake. Research has shown a complex range of public attitudes that are not straightforwardly related to ethnic or religious group[13]. In some countries, premarital screening for certain recessive conditions is compulsory. Although such programmes violate the principle of autonomous informed consent, they may nevertheless have considerable support in some settings. For example compulsory premarital screening for hereditary haemoglobinopathies has been in place since 2004 in Saudi Arabia, and research seems to suggest that more women tend to favour mandatory screening and prohibition of marriage between two carriers on the basis that women may bear more of the burden of caring for a handicapped or chronically ill child than men[14].

Psychological issues

Access to information may result in increased anxiety about a future pregnancy, especially where prospective parents were not formerly aware of potential risks. Conversely, parents who have received preconception care and screening may feel that all risk has been removed and be unprepared for the birth of an affected child. For this reason it is important to make the distinction between those risks that can be reduced or removed and those that cannot.

Prenatal care

Within any setting, the ethical acceptability of prenatal care and screening may be influenced by religious, cultural, or political factors. Policy makers and health providers should

recognise that a range of views may be held and try to find ways of balancing or reconciling conflicts. A number of themes are important:

Equity of access to prenatal care

Around 98% of women utilise prenatal care services in industrialised countries, compared with only 68% women in lower income countries. In many African countries, knowledge and education about safe motherhood is lacking, and there is poor access to healthcare facilities due to factors such as long distances, lack of transport and difficult locations. For women in low-income strata in industrialised countries, psychosocial, structural, and socio-demographic factors are major barriers, while the mother's beliefs about the acceptability of an intervention and the availability of support from others are important motivators.

The legal status and rights of the unborn child

In many countries, laws only provide protection for the child once it is born. The unborn child does not have a legal identity which is separate from its mother. This means that until the child is born, the needs (and wishes) of the mother generally take precedence over those of the unborn child. In many societies, the unborn child is seen as acquiring increasing rights as the pregnancy progresses.

The rights of the pregnant woman and those of her unborn child may conflict during pregnancy. This may be relevant if a pregnant woman knowingly exposes her baby to teratogens such as drugs or alcohol during pregnancy, or refuses treatment that could save the life of herself or her baby.

Protecting the health of the pregnant woman and unborn child

The chances that a woman will have a healthy pregnancy leading to the birth of a healthy child are influenced by a variety of legal, cultural and socio-economic factors. For example, employment legislation may be needed to protect pregnant women against exposure to industrial or agricultural teratogens. Some countries have legal frameworks that acknowledge strict liability for workplace exposures or pollution (to make it easier to bring a successful criminal conviction). Others have statutory authorities that can intervene promptly to monitor and regulate environmental exposures, or laws that provide that vulnerable groups (such as pregnant women) can be excluded from a pool of possible employees without contravening anti-discrimination legislation. It is important to foster a culture of transparency and accountability amongst stakeholders including employers, regulators and workers: workplace monitoring, audit, inspection, and the availability of appropriate, proportionate and enforceable sanctions for any breaches are all important elements. Without these protections, for many individuals, particularly in poorer settings, the benefits of employment may overwhelm the potential health risks particularly where well developed systems of health care, social and economic support are lacking.

A range of legal, regulatory and social measures may be needed to protect women against other dangerous exposures. For example, labelling laws, licensing regimes and dissemination of educational material may raise awareness of the dangers of alcohol to the developing fetus, while smoking may be discouraged by restrictions on smoking in public places, together with educational initiatives and assistance in giving up the habit.

Social and cultural expectations about the role of women may also influence lifestyle, and behaviour. For example, in cultures where alcohol is considered a ‘male drink’, women may be hesitant to truthfully discuss their alcohol consumption and accept (or even be offered) education about the effects of alcohol on the developing fetus. Disclosing details of exposure to other potentially harmful agents such as tobacco, or even disclosing contraceptive use, may be potentially sensitive in some settings.

Implications of prenatal testing and screening

The purpose of prenatal testing is to identify whether the baby is at risk of future ill-health, to lessen those risks and treat any underlying problem if possible, and if there is a prospect of serious disability or disease, to consider the option of terminating the pregnancy, if this is legally and ethically acceptable. As well as highlighting existing health problems, test results may suggest that the child is at risk of developing diseases in the future (possibly, many years in the future as an adult). Test results should be stored in a confidential way, and consideration given to how and when the child might be informed about their risks, and safeguarded against possible discrimination or stigmatisation by others (including employers, insurers or the state).

Informed choice

Emphasis is often placed upon the need for pregnant women to make an informed choice about whether or not to have prenatal tests, and as importantly, how to proceed when the results of the tests are known. It is important that information about testing is provided, before the test, in a non-directive, accessible and supportive manner. Relevant information includes the risks and benefits of the test, as well as any subsequent diagnostic tests that might be required, the available options if the fetus is found to be affected and, if possible, information about the nature and likely severity of the condition(s) tested. Additional support or procedures might be needed to obtain valid consent from those who lack capacity as a result of immaturity, a lack of understanding of local language or through illness or disability.

Prenatal population screening

In countries where there are programmes of universal prenatal screening, certain conditions (such as neural tube defects) tend to be detected as part of an established programme. Subsequent care pathways should document access to supplementary tests or interventions, including access to termination of pregnancy (where local laws and norms permit). Research has shown that a diagnosis made via ultrasound scanning has a much more negative impact than a diagnosis made via biochemical methods. The proliferation of ultrasound scanning services run on a commercial basis (which may not include access to medically qualified professionals) has implications for the way in which diagnoses are made, availability of counselling, and for longer lasting harms to women (including psychological harms).

Prenatal genetic screening programmes which identify babies that are homozygous for a disease such as sickle cell disease or thalassaemia may raise difficult choices about the course of the pregnancy and the ability of the family to support an affected child. Experience from countries having implemented combined prenatal and newborn screening programmes suggests that participants need to be well prepared and better informed about the consequences of screening, and the possible choices to be made.

Screening programmes may also involve testing for infectious diseases, such as syphilis. Delivering screening in this way may be an effective way of targeting scare resources. Where possible, programmes should be organised to provide equitable access to all those at-risk, and for any subsequent treatment that might be required for both mother and child if an infectious disease is diagnosed. Where results are potentially sensitive, they should be communicated in a confidential manner. Sometimes a test result might have implications for other family members (such as siblings of the parents). Ideally, those providing prenatal screening should have protocols for communicating the results of testing to other family members (with the consent of the person being screened). Test results may also reveal unanticipated findings (such as misattributed paternity) and there needs to be processes in place to decide when and how to feedback such results to screening participants.

Termination of pregnancy

Where prenatal screening indicates that a fetus is at high risk of a debilitating congenital disorder, the option of termination of pregnancy may be considered. However, various legal, social and religious issues must be taken into account.

There is wide variation in access to termination of pregnancy. In those European countries where abortion is legal, the rationale for allowing termination of pregnancy is based upon a presumption that as the fetus grows, it acquires increasing rights that should be respected by both individuals and the state (through its polices). Thus termination of pregnancy is more freely available at early stages of pregnancy (the first trimester), but at later stages it may be limited to where a severe condition is detected in the fetus, or the mother's life or health is endangered.

In many places, legal termination of pregnancy is unavailable for religious reasons, or is restricted to cases where termination is necessary to protect the woman's life. In others, diagnosis of a severe congenital disorder may be grounds for a legal termination of pregnancy. For example, a *Fatwa* issued by the Jurisprudence Council of the Islamic World League in 1990 allows abortion in the first 120 days following conception provided that the fetus is affected by a severe malformation that is not amenable to treatment (confirmed by physicians); that a live birth would result in a life of misery for the child and their family, and both parents consent.

The detection of severe congenital disorders early in pregnancy can be problematic where abortion is illegal, as parents face either the harrowing prospect of continuing with the pregnancy in the knowledge that the baby will be stillborn or severely disabled, or resorting to illegal abortion. The wealthy may have the option of safe abortion locally or travelling to access termination of pregnancy in another country or region where it is lawful (so called 'abortion tourism'), but this option is unlikely to be available to the poorest or more educationally disadvantaged. Nevertheless, prenatal detection may still confer an advantage where the pregnancy is maintained, by preparing the family and health services for the birth of a child with a congenital disorder.

Where the majority of procedures are offered illegally, associated costs are often directly related to the poor safety of the procedures[15]. Evidence suggests that unsafe abortion is the cause of around 13% of all maternal deaths, with around 21.6 million unsafe abortions carried out in 2008, most of them in the developing world. The incidence of abortion does not reflect the differences in legal restriction; for example, despite the fact that abortion is illegal in most African countries, the abortion rate is almost identical to that in Europe, where abortion is permitted in many countries. This means that in higher income countries, nearly all abortions are performed safely, whereas more than half of abortions that occur in low and middle income countries are classified as unsafe under the WHO definition (which defines unsafe abortion as a procedure for terminating an unintended pregnancy carried out either by persons lacking the necessary skills or in an environment that does not conform to minimal medical standards, or both)[15].

Psychological issues

For most prospective parents there are likely to be profound psychological consequences from discovering that their unborn baby is affected by a congenital disorder, regardless of their attitude to termination of pregnancy. Even if a false-positive screening result is resolved by a subsequent diagnostic test which shows that the fetus is at no greater than average risk, women may remain anxious about their baby and this anxiety may itself have effects on the developing fetus, and influence maternal behaviour after birth[16]. For some women, a strong religious belief, or fatalism about the course of the pregnancy and about the baby's future health, may be the justification for refusing screening or pregnancy termination even in settings where both screening and pregnancy termination are lawful. However, an important justification for screening and testing before birth is to deal with congenital disorders more

effectively and to avoid discovery once the child is born, which may cause more serious psychological harm to parents than prenatal diagnosis.

Exercising a parental choice to continue with an affected pregnancy

In some high income countries there is sometimes concern that it may be difficult for mothers who have an affected child identified on screening to make a free choice to proceed with the pregnancy in the knowledge of the burden that this is likely to impose upon themselves, their family, health providers and state. These concerns may seem somewhat less relevant in some LMIC where poverty and lack of access to health care and social support may be overwhelmingly important.

Provision of health care in the perinatal period

The absence of health care in the perinatal period constitutes a significant cause of infant mortality and morbidity. Socially and economically deprived mothers, particularly in places with poor health infrastructures, often lack obstetric care that could prevent birth complications that lead to severe disability and neonatal care that could enable timely diagnosis and treatment of congenital disorders. In some countries, lack of access to health care is compounded by preferences for male children over females: thus sometimes claims are made that parents are less likely to seek medical care (particularly if this is expensive and difficult to access) for girls rather than boys.

Newborn

Newborn screening

Newborn screening programmes are ubiquitous in high income countries and the ethical basis for screening for conditions such as phenylketonuria (PKU) and congenital hypothyroidism (CHT) is well documented. The condition screened for must be serious, reasonably frequent, and an effective and reliable test must be available which could be administered on a population basis: If.an affected individual is identified, a treatment or intervention should be available, the programme administered by the state and ideally free of charge[17]. Often, these criteria are not satisfied in many countries[18,].

As with other screening programmes, there is scope for parental anxiety in a number of areas. There is a potential for harm where children are wrongly identified as being at risk (false positives); in some recessive conditions, the health implications of being a carrier may be poorly understood[19]. In particular, parents need timely and appropriate information, and subsequent care should be incorporated within a screening pathway[20].

Treatment and care of disabled people

Those who are born disabled often have a very poor life expectancy, especially in LMIC. This is due to a combination of factors: lack of access to relevant health and social services compounded by social determinants of ill health such as poverty and poor education. Ideally, functional assessments of disability take account of both physical and psychological determinants, as well as social and environmental factors. The effect of severe disabilities may be ameliorated by substantive support from the state. However, this may be virtually non-existent in many settings, where the psychological and economic burden of having a handicapped child falls entirely on the immediate and extended family, and may also have a significant effect on the wider community.

In countries undergoing economic transition, developing state healthcare systems may attempt to provide services for congenital disorders, but the costs can be crippling and raise difficult ethical questions about how resources should be distributed, and the opportunity costs of treating these conditions when there are so many competing demands on limited resources. Ironically, although some treatments may be sufficiently effective to enable

individuals to live independent lives and contribute to the economy. In other cases, decreasing mortality may mean many more years of expensive care. For this reason, many countries are focussing on preventive strategies, and grappling with the ethical issues raised by compulsory measures such as preconception screening for carrier status for recessive genetic conditions.

CONCLUSIONS

The many ELSI questions that arise from the care and prevention of congenital disorders can rarely be considered in isolation, but form a web of interconnected issues that may be challenging to analyse and address. Nevertheless, it is important that all those who are involved in the planning, implementation and evaluation of programmes and services regard these issues not as theoretical considerations of interest only to philosophers and ethicists, but as central issues that they must take into account in their own clinical practice and decision-making.

Consanguinity

Introduction

The term consanguinity is used to describe a relationship between two people who share one or more common biological ancestors. A consanguineous couple is most commonly defined as being related as second cousins or closer and this is often used as a working definition in the clinical genetics setting[1]. Figure 1 shows that many regions of Asia, the Middle East and North Africa have a high prevalence of consanguineous marriages. Recent estimates indicate that some 10.4% of the world population are either married to a biological relative or are the progeny of a consanguineous union[2]. This estimate is believed to be conservative due to the sparse data available in populous countries located in regions with high prevalence of close kin marriage.

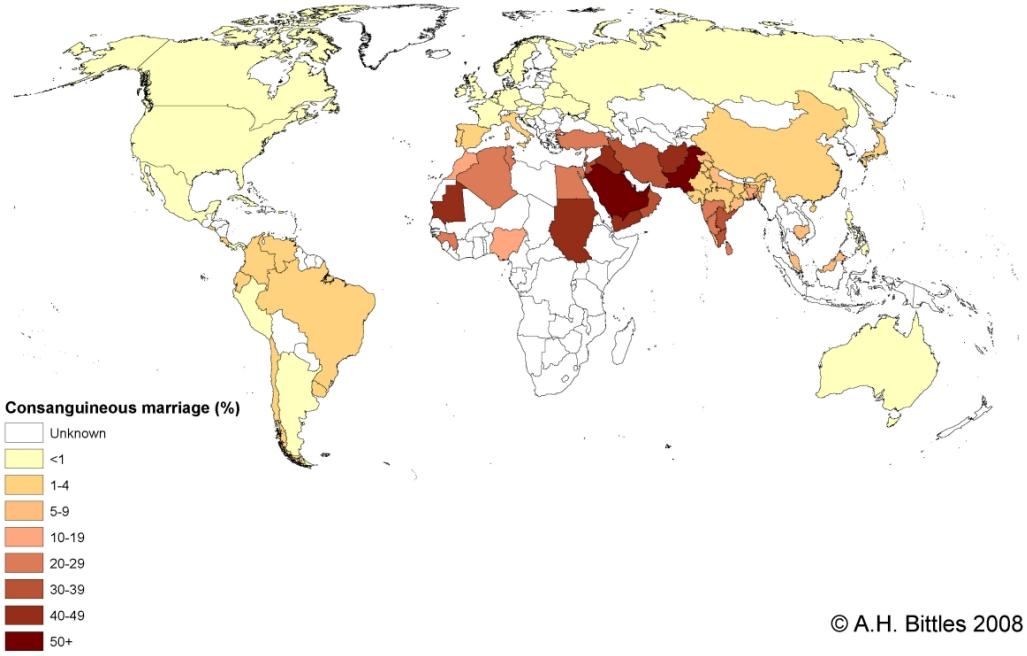


Figure 1: A broad-scale map of the current global prevalence of marriages between couples related as second cousins or closer (available from http://www.consang.net).

Consanguineous marriages are not just confined to these developing regions, but have in fact been a part of many westernised societies for a long time, with famous first cousin marriages such as Charles Darwin and Emma Wedgewood, and Albert Einstein and Elsa Einstein. In the Western world, as recently as the mid-19th-century, cousin marriage was socially accepted and often widely favoured, especially amongst the more privileged classes[2;3]. Given this situation, it is interesting how marriage between close relatives is now subject to widespread negative opinion and prejudice within western society. Many societies[2] have placed restrictions on marrying relatives, although the degree of relationship that is

[2] First cousin marriages are permissible under the Marriage Act 1949 in English Law, and under civil legislation in other European countries. However, they are prohibited in 31 of the 50 states of the USA, in the People's Republic of China, and the People's Democratic Republic of (North) Korea[4].

prohibited varies. All current societies forbid marriage between first degree relatives, such as siblings, and many also forbid relations between second degree relatives (e.g. uncle-niece).

Health and reproduction

In spite of some biological plausibility for reduced fertility in consanguineous marriages, a meta-analysis of studies conducted in different countries shows a higher mean number of children born in all categories of consanguineous marriage when compared with non-consanguineous marriages[4;5]. This finding may partly be explained by the lower parental age and age at first birth of consanguineous couples[6], and the use and uptake of contraception may also be lower in consanguineous couples[7].

Much attention has focused on the adverse health effects associated with consanguinity. Evidence linking consanguinity to increased rates of spontaneous abortion or stillbirths is mixed[8-11]. Recent work has reported that among the offspring of first cousin couples there are 1.5% more stillbirths, 1.1% more neonatal deaths and 1.1% more infant deaths than among the progeny of non-consanguineous couples. However, these figures may be compromised by inadequate control for non-genetic factors as well as a small number of studies identified as outliers[12]. In general, there has been a tendency to exaggerate and oversimplify the impact of consanguinity, and to give less weight to other social or geographical factors which impact upon population subdivision, such as the *biraderi* membership (inherited occupational lineages) in Pakistan[12].

Consanguinity presents a broad and complex picture from a health perspective, involving major social, economic, and demographic influences, as well as differential reproductive behaviour and other causes of early- and late-onset morbidity and mortality (Figure 2)[2]. It is necessary to understand and control for the influence of these non-genetic variables before addressing needs on a genetic basis.

Although these caveats must be kept in mind, a significant positive association has been consistently observed between consanguinity and morbidity, as well as a higher prevalence of congenital disorders amongst first cousin marriages[12]. Excess rates for congenital disorders amongst marriages between first cousins have varied from 0.3% to 10.0%, with a mean and median value of 4.1% and 3.3% respectively (A Bittles, personal communication). This variation is largely due to different study protocols and diagnostic facilities, varying sample sizes, and limited control for sociodemographic variables[12].

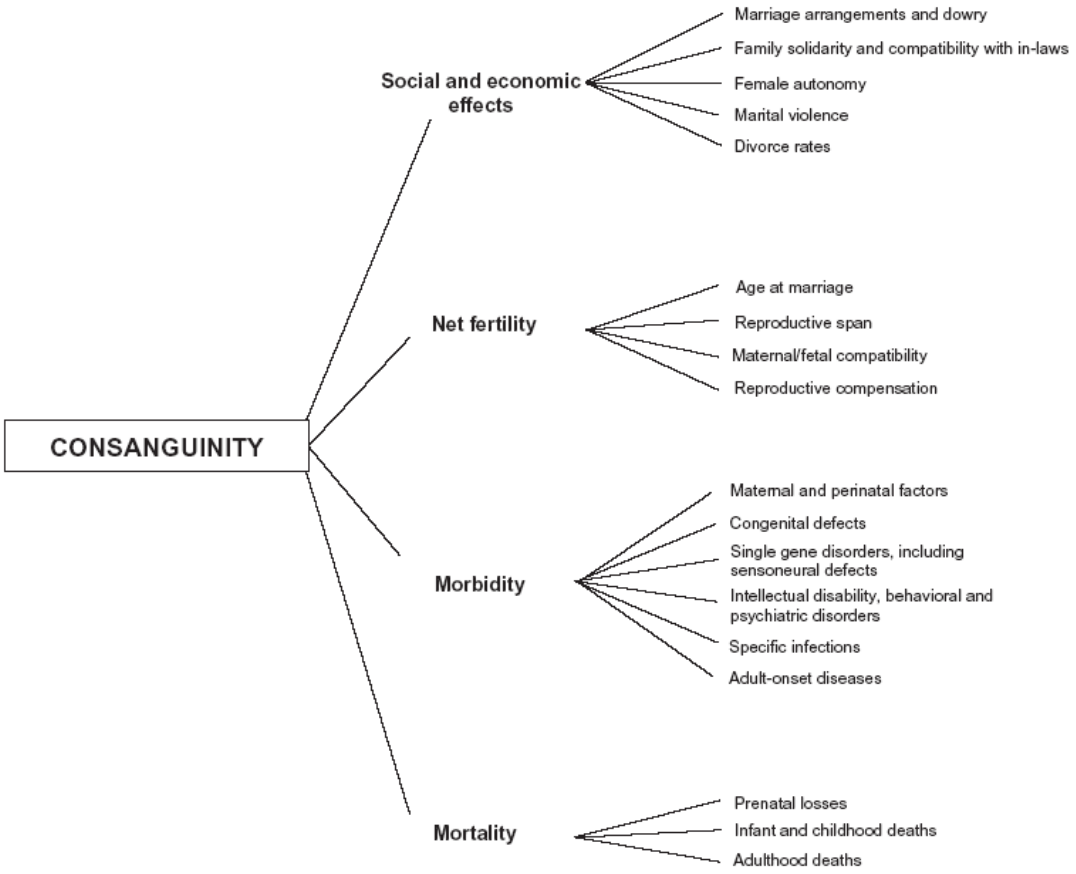


Figure 2: Influences and outcomes of consanguineous marriage, taken from Bittles and Black[2].

The increased levels of morbidity and mortality in populations with increased rates of consanguineous marriages are caused by the detrimental action of rare, autosomal recessive genes inherited from a common ancestor. Examples include the alleles causing sickle cell disease and familial recessive deafness, which have higher frequencies in the offspring of consanguineous marriages compared to non-consanguineous couples. The rarer the disorder the greater the proportional influence of consanguinity on its expression[1;12]. (It should be noted, however, that due to founder effects and random genetic drift, alleles which are rare in large populations can still increase to high frequencies in populations of limited size even in the absence of preferential consanguineous marriages.) At the population level, an excess birth prevalence of 2-4% is widely cited for autosomal recessive conditions in the offspring of first cousin marriages, although for individual couples this may vary from 0-25% or higher[13]; this applies equally to consanguineous and non-consanguineous couples where both parents are carriers of the recessive allele in question. Consanguinity may also confer a 2-3 fold increase in risk for a broad range of congenital heart disease phenotypes[14-18] although data are both limited and problematic due to poor phenotyping.

For the purposes of the Modell Global Database of Constitutional Disorders (B Modell, personal communication), the rate of increment in autosomal recessive disorders by consanguinity was based on the increase in prevalence of recessive disorders observed in the Birmingham, UK study conducted amongst British Pakistanis[19]. The increase in congenital disorders used is 7 per 1,000 increment for every 0.01 increase in population coefficient of consanguinity, i.e. a calculated increase of 44/1,000 births in couples related as first cousins (F = 0.0625). However, a limitation of these estimates is that they are based on

the assumption that the Birmingham Pakistani community is socially and genetically homogeneous and this is not likely to be the case (A Bittles, personal communication).

Reducing adverse health outcomes

To help overcome the increased health burden presented by consanguineous marriages, strategies focusing on several factors can be put in place. At the population level, public education may focus on genetic diseases and the effect of consanguinity, as well as providing information on the availability of preventive measures[20]. In addition to education, prevention may include premarital and preconception carrier testing for more common conditions at a community-wide level, with genetic counselling to inform couples on genetic risks. Preimplantation genetic diagnosis and prenatal genetic diagnosis, in conjunction with the option of termination of pregnancy (where acceptable on religious, ethical, and legal grounds), are strategies carrier couples may use to reduce their risk of having a child affected by a genetic condition[20].

However, a population-based approach may be inappropriate or insufficient in populations where consanguineous marriages are an integral part of cultural and social life. Here, the focus should be shifted to the identification of families and sub-communities at increased risk[21].

For a particular recessive condition, couples who are consanguineous fall into two categories: a majority who not both carry the same recessive allele, and a minority who do and thus have a 25% risk of an affected child being conceived in each pregnancy. The task should be to identify this minority group at increased risk. In a population where the prevalence of consanguineous marriage is low, at-risk couples may be brought to medical attention through their first affected child (the index case). In a population where consanguineous marriage is common, this index case would also help to identify further at-risk couples in the wider family. Taking an extensive family history where recessive genetic disease is suspected would allow carriers to be identified on a systematic and large-scale basis. Couples could then be identified prospectively, although this family-orientated approach may be difficult to implement[21], and could lead to some adverse and unintended outcomes, e.g. in terms of health and life insurance cover.

The most effective and comprehensive strategy for addressing the effects of consanguinity might be to offer a range of approaches delivered at a variety of different levels including the family or tribe[22], the community and the wider population.

It is important to be aware that while close kin marriages provide a mechanism for the expression of rare recessive disease genes, they are not in themselves the *cause* of genetic disease. Special care should be taken not to stigmatise or discriminate against consanguineous couples or their children[23].

Social and economic factors

In various parts of the world, the social custom of consanguineous marriage is deeply entrenched. These marriages account for a large proportion of the marital unions in regions throughout the Eastern Mediterranean, Central Asia, North Africa, sub-Saharan Africa, the Indian subcontinent, and some parts of South America, as illustrated in Figure 1. Geographical or social isolation of minority and migrant groups can also lead to increased homozygosity following consecutive generations of marriage within the community, even in couples who are not known to be genetically related, with an increase in the frequency of particular genes within a population.

The preference for consanguineous marriage seems to be both social and economic[7;24] (Box 1). From a social perspective, the traditional practice of marriage between cousins is maintained in order to strengthen family ties and retain property within the family unit[24]. The

families know each other's social and financial backgrounds, reducing the uncertainties that might arise through marriage outside the family or community[24]. Other perceived benefits include improvements in the position of women and increased female autonomy in patriarchal societies[25]. The financial advantages of consanguinity include reduced payment of dowries, ease of marital arrangements and a potentially closer relationship between the bride and her in-laws, which in turn can lead to more stable and durable marriages and lower divorce rates[7;25].

Globally the highest numbers of consanguineous marriages are amongst the poor, rural and largely illiterate communities[1]. For these reasons, interactions between consanguinity and other social variables can potentially complicate any assessment of the genetic effects of human inbreeding. Failure to account for such social variables when estimating the possible effects of consanguinity on early mortality would lead to biased results, with overestimation of the adverse biological effects associated with cousin marriage[5]. Conversely, if consanguinity is not included as an explanatory variable, adverse birth outcomes and early deaths may mistakenly be ascribed only to other more widely or straightforwardly investigated variables such as maternal age, maternal education, birth interval or birth order.

Box 1: Taken from Saggar and Bittles[25].

Social and economic advantages of consanguineous marriage
Assurance of marrying within the family and the strengthening of family and societal ties
Assurance of knowing one's spouse before marriage
Reduced chances of maltreatment or desertion
Simplified premarital negotiations, with conditions and arrangement agreed in late childhood or early teens
Greater social compatibility of the bride with her husband's family, particularly her mother-in-law who is also a relative
Reduced requirement for dowry or bride wealth payments, with maintenance of the family goods and monies
For land-owning families, maintenance of family land-holdings which otherwise may be subdivided by inheritance.

APPENDICES

The coefficient of relationship (*r*) is the proportion of genes identical by descent shared by two individuals. It can be calculated as follows:

$r = (1/2)^n$

where n is the number of steps apart on a pedigree for two individuals via their common ancestor. For example, two first cousins who share a grandparent:

$r = [(1/2)^4] + [(1/2)^4] = 1/8$

The coefficient of inbreeding (*F*) is the probability that an individual receives at a given gene locus two genes that are identical by descent (i.e. that they are inherited from a single gene carried by a common ancestor. It can be calculated as follows:

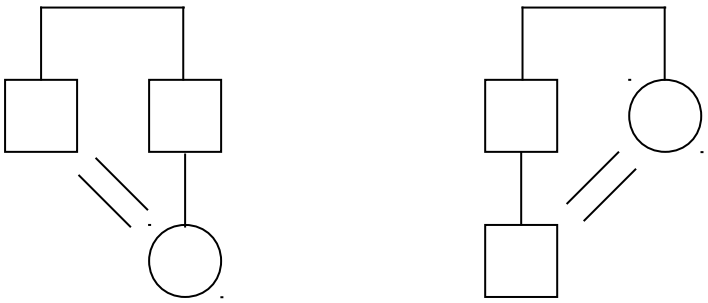
$F = \sum (1/2)^n (1+F_A)$

where n is the number of steps apart on a pedigree for two individuals via their common ancestor and F_A is the common ancestor's coefficient of inbreeding. Examples of inbreeding coefficients are shown below.

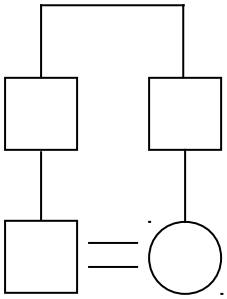
Types of consanguineous marriage and their inbreeding coefficient

Below are some of the more common consanguineous marriage pairings although they can also be more complex with many of these pairings occurring across several generations of larger extended families.

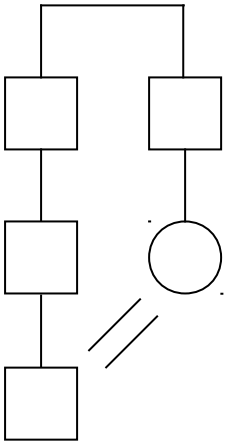
Uncle-niece, aunt-nephew marriage *F* = 0.125 (1/8)



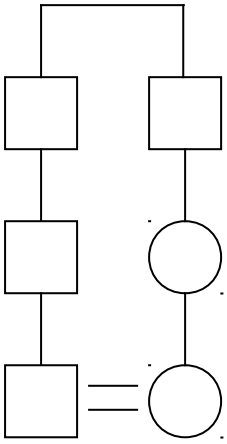
First cousins *F* = 0.0625 (1/16)



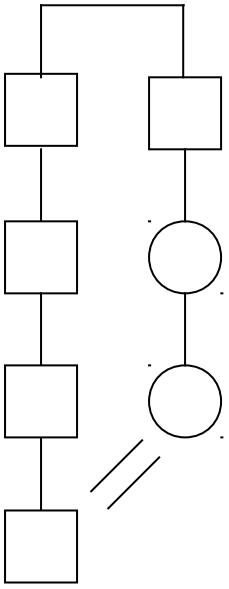
First cousins once removed *F* = 0.0313 (1/32)



Second cousins *F* = 0.0156 (1/64)



Second cousins once removed *F* = 0.0078 (1/128)



Third cousins *F* = 0.0039 (1/256)

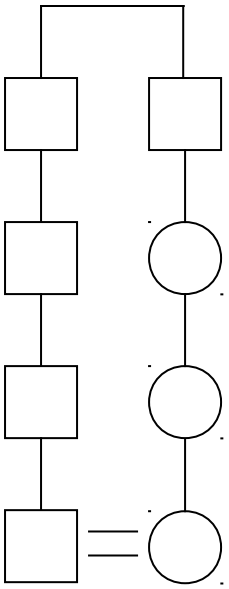


Table 1: Proportion of genes shared between close blood relatives

Relationship to each other	**Relationship type**	**Proportion of genes they have in common**
Identical twins (monozygotic)		All (1, 100%)
Brothers and sisters, non-identical (dizygotic) twins, parents and children	First-degree relatives	Half (1/2, 50%)
Uncles and aunts, nephews and nieces, grandparents and half-brothers and half-sisters	Second-degree relatives	Quarter (1/4, 25%)
First cousins, half-uncles and half-aunts and half-nephews and half-nieces	Third-degree relatives	Eighth (1/8, 12.5%)

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Engaging Patients

The importance of engaging patients

Patient organisations can play an important role in the development of services. One such example is the LAM Foundation, a support group set up for people affected by lymphangioleiomyatosis, a rare condition which causes progressive loss of lung function in young women (Ingelfinger and Drazen 2011). The group was originally set up by the mother of a woman with the condition, as she realized that very little was known about the condition. The support group were then able to effectively raise money and obtain third-party funding for research into the biology of the condition. Through the support group, research scientists were able to access patients to take part in clinical trials. This in turn led to successful treatment trials.

Other reasons for engaging patients in service development include the following:

Patients and health professionals may differ in their views on which aspects of services, care and treatment they consider valuable. It is important to ensure when developing services that they meet people's needs and that the health service does not spend money on inappropriate services.

By consulting with patients, health professionals and service developers can ensure that the decisions and actions they make are patient centred and put the needs of service users first. Moreover, they can ensure that services are equitable and respond to the needs of the community.

Patients have a unique understanding of their condition. Service developers can gain valuable knowledge and insight about services by tapping in to their expertise.

It is important to recognise the rights to which patients may be entitled as recipients of healthcare, including decisions about services which affect them.

Services are more likely to be effective if the patient is considered an active partner in healthcare decision-making than if they are viewed as someone who is solely a recipient.

Research has shown (Crawford 2002) that there are numerous benefits associated with involving patients in service development, which result in higher-quality services overall. These include:

Improvements in people's health;

Increased satisfaction with care;

Services becoming more accessible;

Increased patient empowerment leading to greater responsibility over healthcare;

Improvements in staff patient relationships and increased trust;

Production of new or improved sources of information for patients and families;

Reduced levels of complaints.

Involving patients in a health needs assessment: levels of patient engagement

Patients, health professionals and service developers may have very different perspectives and opinions on the key needs and priorities of health services. It is important to keep this in mind when engaging various stakeholders in a health needs assessment in order to balance the different expectations that each member will have.

Before you begin recruiting patient representatives, it is important to consider the different levels of patient engagement that will be necessary for the HNA. You will want to recruit 'expert' patients, who are patients with high levels of knowledge or expertise regarding their particular condition and/or patient representatives who may or may not be patients themselves but represent a particular group of patients or conditions. Their role will be to ensure that the opinions of patients are heard during the HNA process and identify areas where patients' preferences and choices may need to be acknowledged. You will need to distinguish from the outset if and which patient representatives may be members of the Coordinating Team, and which will form part of the HNA and then the prioritisation teams. This may depend in part on their level of expertise, but also how much time they have available.

You will also want to recruit 'service user informants'. These are service users such as patients or parents, who are not in the coordinating team or stakeholder group, but whose role is to provide the evidence for service users' views, experiences and preferences that will help inform the HNA and prioritisation process.

Recruitment into the coordinating team and/or stakeholder group

When forming a team, you will want to involve 'expert' patients and patient group representatives who will be able to provide a good overview of the issues important to patients and their families. When setting agendas for meetings, the co-ordinator will need to ensure patients are given the opportunity to be fully involved in discussions and their comments acknowledged and considered and taken on board.

Whilst 'expert' patients and patient group representatives do not need to have any formal qualifications, you should try to include people with a range of expertise. This may include people who:

Are from an 'umbrella' organisation which represents a range of conditions and/or patient group representatives with an understanding of more specific conditions;

Represent a sample of diseases, e.g. lethal in utero/ neonatal; recessive; late onset dominant; sex linked; metabolic; neurological etc.;

Have a degree of knowledge and understanding of the condition;

Have time to commit to the work, aptitude to transmit their opinion and ability for team-working.

There are a number of ways to go about recruiting patient representatives. These include:

Contacting an 'umbrella' organisation or patient group. The directors of these organisations may be able to participate themselves; alternatively they should be able to nominate a member(s) who they feel would be suitable. A good starting point for identifying appropriate organisations is the International Alliance of Patient Organizations (www.patientsorganizations.org).

Speaking with health professionals who may know of relevant patient or umbrella groups that you could recruit through, if you do not know of any yourself.

Advertising from within the clinic or hospital. This may be through posters, leaflets, or through the departmental website.

It is important to clarify from the outset what role you expect the patient representatives to play, what support they will be given and the commitment required of them.

Recruiting service user informants

To gain an in-depth understanding of the local needs and priorities of service users, it is important that you speak to them directly. You will also want to ensure that you hear from a variety of service users so that the information you receive is representative of the community at large and not one particular viewpoint. Here are some things you should consider when recruiting service user informants. Ideally, you will want a mix for each of these sub-groups.

Level of education (low level of education – high level of education)

Health literacy: an individual's ability to read, understand and use healthcare information (poor – high)

Geographical location (rural – urban)

Socio-economic status (rich – poor)

Ethnicity

Religion

Gender and age group

There are a number of ways to go about recruiting service informants, such as:

Through 'umbrella' organisations or patient groups. These organisations will be able to recruit their members directly by telephone, letter, email, their website, newsletter or face to face.

Physicians may be able to recruit patients by searching their hospital archives or database. This may require that they first gain permission from the hospital /ethics committee to ensure issues of confidentiality are addressed. If and when permission has been granted, potential participants can be contacted e.g. by letter, to see whether they would be interested in taking part;

Through community or religious centres. Again, this may be through a poster or leaflet explaining what a health needs assessment is, why it is being conducted and how they can get involved.

How to identify service user needs, views and preferences/priorities

In order to inform the HNA, you will want to explore some of the key issues affecting service users. For example, you might want to identify patients' experience of the health service and how the service meets or does not meet their needs. Or you might want to investigate which areas they believe to be most important in the delivery of services, or what suggestions patients have for developing or improving services. It may be a good idea to write down a list of key questions you wish to address at the beginning of the process. It is important that this is done with the help of the patient representatives to ensure the questions are relevant and appropriate.

There are a number of ways of identifying service users' needs and priorities. Which you decide to use will depend on how many people you want to hear from, what time, resources and support you have available and what level of detail you want to go into. Here is a brief overview of some of the different methods you could use (to insert reference here, or in each method, if there are from different sources).

One to one interviews

These usually involve just the interviewer and the patient or parent/relative, although partners might also be present. Interviews may be variable in length, for example they could

last between half an hour and an hour and can be conducted over the telephone or face to face. The interviewer will usually record the responses either by audio recording the interview or taking written notes. Interviewers will usually have a list of questions they wish to ask or broad topics they want to explore. Questions might alter or be added to during the interview if new areas of interest emerge during the interview and are uncovered.

Interviews are a useful tool if you want to explore new areas of interest or want detailed information about a particular question or issue. However, they can be time consuming to conduct and so are most appropriate where you want in-depth information from a small number of people. It is important to address the issue of consent before conducting an interview. Issues to discuss include permission to record the interview, and whether the person being interviewed is happy for their comments to be identifiable or wants to remain anonymous. The need for consent also applies when conducting focus groups.

Focus groups and group interviews

Focus groups are a form of group interview and are a convenient way of collecting information from several people at the same time. Participants are also encouraged to explore areas more widely than they might otherwise have done in an interview, as a result of interacting with other participants. The ideal size is from four to eight people and sessions may last one or two hours. As in individual interviews, there will usually be a number of set questions or topics the person conducting the focus group will want to explore. It is important that whoever is running the group is able to ensure that the conversation does not stray too far away from the topic. Ideally, the group's discussion will be audio taped or, alternatively, written notes can be taken as long as consent is given. If notes are going to be taken, it is a good idea that this is done by someone other than the person leading the discussion.

Focus groups, like one-to-one interviews, can be useful as they do not discriminate against people who cannot read or write. They can also encourage participation from those who are reluctant to be interviewed on their own. One disadvantage is that participants have to come together on an arranged day, and this can be difficult to coordinate. Another is that the discussion might be dominated by stronger speakers. The person running the focus group should try to encourage all members to contribute equally.

Gender and ethno-cultural traditions can be accommodated within the one-on-one interviews and focus group modalities. Moreover, consideration of the gender, age and ethno-cultural composition of groups and the moderator frequently yields more useful findings especially when there are strong traditions which may inhibit meaningful participation of specific groups.

Questionnaires

A questionnaire is a list of questions designed to collect specific information. The questions can be open-ended, which means that there are no pre-set response choices, or closed whereby there are pre-coded responses which the respondent must choose from. Pre-coded questions may include a variety of response formats including yes/no response choices, multiple choices (no restriction on the number of responses that can be ticked) or scaled responses (such as rating responses on a scale of 1-5). Closed questions are more suitable for topics about which much is known, and are quicker to analyse, although they carry the risk that replies may be forced into inappropriate categories. Open-ended questions are preferable where replies are unknown, too complex or numerous to pre-code.

It is important that questionnaires are clear and easy to comprehend, and that all possible options to a question are covered. Therefore, it is essential that questionnaires are tested or 'piloted' with a small number of people before they are distributed or applied more widely.

Questionnaires are a relatively inexpensive way to gather data from a potentially large number of respondents. However, the disadvantage of using them is that they may

discriminate against people who cannot read or write, unless they are conducted as telephone or face to face interviews. Data manipulation and storage may also pose complications depending on the computing services available. Confidentiality of response is also a necessary element and condition which needs to be in place regardless of the data collection techniques used.

Supporting patients and their representatives and ensuring their perspective is heard

It is important that patient representatives are supported during the HNA so that they can contribute fully in their role. There are a number of ways of achieving this. These include:

Providing them with sufficient background information well in advance, and providing assistance if necessary, to ensure they can be fully engaged in developing and implementing plans around priority issues. This may include providing them with information about how services are run, what the cost implications of different services are, what the limitations of services are including the reasons behind these limitations (e.g. technical, ethical, economic etc.) and legal aspects that might affect service delivery (e.g. whether termination of pregnancy on grounds of congenital disorder is a legal option).

Ensuring meetings include a critical volume of patient representatives to balance the influence that more 'expert' stakeholders such as policy makers or health professionals might exert.

Ensuring that the coordinator has an awareness of the hierarchies that may exist within the group and has the skill to facilitate discussions in a way that enables all group members to participate in full.

Providing an opportunity before the meeting for patient representatives to discuss any uncertainties they may have about the content of the meeting or the procedures to be followed;

Following up after meetings with patient representatives to ensure they felt that their perspective had been listened to and understood why their views had not been adopted if this was the case.

Ensuring patients are not out of pocket as a result of their participation in the exercise, e.g. by reimbursing travel costs.

Accommodating any special needs and communication support needed to ensure all participants can contribute equally and effectively.

Ground rules

Ground rules should also be set at the beginning of any workshop or meeting to enable the group to work together efficiently and effectively. Whilst each group should agree upon their own rules of engagement at the outset, here are some suggestions that you might wish to include:

There will remain at all times an atmosphere of mutual respect within the group and members will listen to each other.

There will be an open and friendly atmosphere within the meeting, with all participants encouraged to contribute equally.

There will be no retribution for raising difficult or controversial issues, or for disagreeing with other participants.

No one person or group of people will intimidate others or not allow the views and opinions of others to be heard.

Only one person will speak at a time.

When someone is speaking they should be allowed to finish without being interrupted.

If a comment is unclear to any member of the group, that person should ask the speaker to repeat or explain it.

Ground rules such as these should ensure open, respectful dialogue and maximum participation.

Key questions

Here is a list of questions you might want to think about before you begin engaging patients in the HNA.

Which patient groups exist in my country that might be relevant for this exercise?

How will I go about finding them?

How will I involve them?

How much time and involvement will be expected from them so I can let them know this beforehand?

Will I be able to reimburse them for their time and travel costs?

What are the key issues I will want them to consider?

How will I ensure their concerns are listened to?

GLOSSARY

Service user informant – a service user such as a patient or parent whose role is to provide the evidence for service users' views, experiences and preferences.

Expert patient – a patient with high levels of knowledge or expertise regarding their particular condition.

Umbrella organisation – an organisation which represents a range of organisations or conditions.

Patient representative – someone who represents a particular group of patients or conditions.

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Health Economics

Introduction

Health economics is the discipline that attempts to address the problem of scarcity of resources in the health care setting and uses economic evaluation as a method of informing decisions; for example, on which health intervention or service to fund from the limited resources that are available. It can be thought of as the application of economic theories, concepts and evaluation techniques to the health sector. Information regarding the effectiveness of an intervention is normally not sufficient on its own for decision makers to decide which intervention to implement. Cost-effectiveness is also important when considering the opportunity costs (that is, the benefits that are foregone) in choosing one course of action over another. Economic evaluation is a set of analytical approaches that are used to describe and compare the costs and benefits of competing uses of resources in order to make a value judgment on which use provides better 'value for money'.

TYPES OF ECONOMIC EVALUATION

Drummond *et al*.[1] have defined economic evaluation as "*the comparative analysis of alternative courses of action in terms of both their costs and consequences*". At its most basic level it includes the need to identify, measure, value, and then compare these costs and benefits. The three types of full economic evaluations are cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), and cost-utility analysis (CUA). These three methods differ in the way each one measures the outcomes of the intervention under evaluation. Another commonly used partial economic evaluation is cost-minimisation analysis (CMA) which assumes the outcomes to be similar and focuses on cost.

CBA: both costs and benefits (health and non-health) are measured in monetary units. Results may be presented in the form of a cost-benefit ratio or as a monetary value representing the net benefit or loss entailed in choosing one programme over another.

CEA: interventions with a common outcome, often in natural units (such as number of cases diagnosed or cases prevented or life years lost/gained), are compared to determine which intervention maximises the outcome for the same input to produce a cost per outcome unit (e.g. cost per diagnosis).

CUA: measures outcomes of alternative interventions in terms of a more generic utility measure. Quality-adjusted life-years (QALYs) gained incorporates length of life and health status into a single metric with results presented as cost per QALY. Disability-adjusted life-years (DALYs) avoided combines the years of potential life lost due to premature death (burden of mortality) and the years of productive life lost due to disability (burden of morbidity) into a single metric with results presented as cost per DALY (e.g. 1 DALY represents one year of healthy life lost or two years of life lost at 50% quality of health, etc.).

CMA: this method can be used when two or more evaluated alternatives produce outcomes (health effects) that can be argued to be sufficiently similar or equivalent. The choice between alternatives then comes down to costs, with the least costly chosen[1].

Estimating costs

Regardless of which method of economic evaluation is undertaken, costing methodology is a common feature. Costs can be thought of as the value of resources required to produce a service or good. There are three key steps in a costing analysis: first, the identification of costs in terms of which resources might be affected by the programme or intervention; second, the measurement of costs identified as important (a further question arising here is

how to monitor the levels of resource use); and third, the valuation attached to each of the resources.

Costs can be categorised into two: tangible costs and intangible costs. Tangible costs can be further broken down into direct health service costs, non-direct health service costs, and indirect costs. Direct health service costs would include costs associated with a preventive service or intervention (e.g. vaccination, fortification of foods, preconception visit and education), the health care service or intervention itself (such as cost of surgery), costs of clinic visits and any resulting hospitalisation, costs of obtaining results, costs of confirming results (possibly using a different method), cost of genetic counselling, costs of any resulting follow-up tests and also costs of any intervention used. Non-direct health service costs include any costs that are incurred as a result of the programme or intervention but are not directly related to the medical care itself. Examples include the costs incurred by the patients (for example the cost of travelling to the clinic), administration costs, utility (e.g. electricity) costs and overheads. The direct and non-direct costs can be grouped together.

Indirect costs can be thought of as losses in productivity or resources foregone by the patient or a carer as a result of participating in the programme or intervention. Examples include reduced productivity as a direct result of the condition itself or the side effects of treatment and time lost in participating in the programme or undertaking the treatment. For a young child, parents or carers also suffer productivity loss by having to take their child to clinic for diagnosis and subsequent treatment as well as having to look after the child at home.

Intangible costs can be thought of as the emotional costs associated with anxiety, pain and suffering as a result of having the illness or disability, from information received or the side effects of the intervention itself. These costs are often difficult to quantify and value and so are often just excluded in economic evaluations.

Because individuals prefer to incur costs in the future rather than now, and gain benefits sooner rather than later, it can be argued that costs and benefits that occur at different times should not be given the same weighting. In order to account for this time preference and opportunity cost, costs incurred in future years should be discounted by using the formula $Cp = \sum_{n=0}^{N} \frac{Cf_n}{(1+r)^n}$ where Cp is the present value of costs, Cf_n is the future cost at year n (e.g. if an intervention is expected to last for 5 years then you could use n=5), and r is the discount rate (e.g. often set at 3% per year but can vary depending on what the expected rate of return would be if, for example, you put the money into a bank account).

Estimating health outcomes

Mortality and morbidity are the most commonly used measures of health. The mortality rate is simply a measure of the number of deaths in a given population per unit of time, often expressed as deaths per 1000 individuals per year. The mortality rate is a fairly insensitive measure of health and doesn't provide an account of the health outcomes that do not actually result in death. Morbidity is often used to refer to incidence rate or disease prevalence, which measure respectively the number of patients with a given disease/condition in a given population per unit of time (often expressed as number with disease per 1000 individuals per year) or, for prevalence, number with the disease at a given time.

For a cost-effectiveness analysis, it may be simplest to use health outcomes that are easy to identify and measure, such as the number of cases detected or the number of cases treated. Other outcomes of interest may include reduction in pain or the number of lives or life years saved. Quality of life and length of life combined can be measured in metrics such as DALYs/QALYs and are described briefly below. Health outcomes in future years should also be discounted, in the same manner as costs (mentioned above).

DALYs

The disability-adjusted life year (DALY) is a health gap measure that combines both the time lost due to premature mortality and the morbidity associated with a non-fatal condition[2]. One DALY can be thought of as one lost year of 'healthy' life and is described in detail by Murray and Lopez[3]. It has been used by the Global Burden of Disease and Injury study as a measure that quantifies the burden of disease in a metric that can be used for cost-effectiveness analysis. DALYs for a disease/condition are calculated as the years lost due to premature mortality (YLL) in the population plus the equivalent 'healthy' years lost due to disability (YLD) for incident cases of disease/condition. A more detailed description of how to calculate DALYs can be found in chapter 11 of the WHO National Burden of Disease Manual[2].

DALY = YLL + YLD

YLL

The Years of Life Lost (YLL) is most simplistically calculated by multiplying the number of deaths (N) by the average life expectancy at the age at which death occurs (L). This measure attempts to account for the premature mortality in a population due to a given disease/condition.

YLL = N x L

YLD

The Years Lost due to Disability (YLD) is used to estimate a health status associated with a given disease/condition for a particular time period. It is most simplistically calculated as the number of incident cases in that time period (I) multiplied by a disability weight (DW) which reflects the severity of disease on a scale of 0 (perfect health) to 1 (dead), multiplied by the average duration in which an individual is in that disease state until either remission or death (L).

YLD = I x DW x L

QALYs

The Quality-Adjusted Life Year (QALY) is a generic metric designed to combine a measurement of both the quality and the quantity of life[4]. Utility preference scores which are used to measure QALYs generally range between 0 (death) and 1 (perfect health) although there can be health states that are scored as worse than death with a score of less than 0. Utility scores can be elicited using standardised instruments that attempt to measure health outcomes via a questionnaire such as, for example, the EuroQol 5 Dimension descriptive system questionnaire (EQ-5D). The EQ-5D is a generic measure of health-related quality of life, mapping respondents onto a health state that is defined by five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) in which each of the five dimensions has 3 levels of severity (level 1 = no problems, level 2 = some problems, and level 3 = extreme problems). This creates possible health states at each dimension with 243 theoretical possible health states (3^5 = 243) plus two further states for completeness (unconscious and dead) to give 245 possible states. These states are then valued by members of the public to allow a societal value to be placed upon the health states on a scale of 1 "full health" to 0 "death" from which QALYs can then be calculated. One QALY can be thought of as a single year of life in perfect health or two years in a 0.5 health state etc.

Comparing costs and health outcomes

Once the costs and health outcomes (effects) have been identified, measured and valued, a joint assessment of these two outcomes for both interventions being evaluated is required in order to determine what the incremental value is of the new intervention or service and its effect on health compared to the current (old) intervention or service.

The incremental cost-effectiveness ratio (ICER) is a method for comparing the cost and effect of two interventions using the formula $\frac{Cost_A - Cost_B}{Effect_A - Effect_B}$ where $Cost_A$ is the mean cost of intervention group A, $Cost_B$ is the mean cost of intervention group B, $Effect_A$ is the mean effect for intervention group A and $Effect_B$ is the mean effect for intervention group B[5].

Economic evaluation relies on assessing incremental costs and incremental benefits. The decision problem can be thought of as a 3x3 table where a new treatment is worse, the same or better than the current treatment. Costs too can be higher, the same or lower than of the existing intervention. We can then get some indication of the potential cost-effectiveness as indicated in Table 1. If a new intervention has a better outcome and a better (lower) cost than the new intervention, it is better value than the existing intervention and should be accepted. If the new intervention is both more expensive and has a worse outcome then it can be rejected in favour of the existing intervention. If the new intervention is more expensive and has a better outcome, then a decision is required as to whether this estimate for the cost-effectiveness ratio is above or below willingness-to-pay (which can be thought of as the maximum that someone would be willing to pay, exchange or sacrifice in order to receive a benefit or to avoid harm). If above this threshold, then the new intervention can be rejected but if below then the new intervention can be accepted.

Table 1 Simple tabular form of a cost-effectiveness plane

Costs	**Outcomes**		
	Worse	**Same**	**Better**
More expensive	Reject	Reject	Consider?
Same	Reject	Consider?	Accept+
Less expensive	Reject	Accept+	Accept++

Decision making

Multi-Criteria Decision Analysis

The use of multi-criteria decision analysis (MCDA) may facilitate evaluation in situations where several goals other than cost-effectiveness can be incorporated into the decision-making process, such as equity and acceptability to patients. It is a useful technique for deciding on resource use both between programmes and within them. It is widely used by economists for resource allocation decisions and priority setting but can equally be used for inter-programme resource allocation, where greater technical efficiency is required. Rob Baltussen and Louis Niessen[7] provide an excellent introduction to, and case for, the use of MCDA in healthcare decision making of all kinds, including allocation polices in developing countries[3].

Program Budgeting and Marginal Analysis

Programme budgeting and marginal analysis (PBMA) is an approach that can be used for priority setting based on the same principles as economic evaluation but in a more pragmatic manner and across various levels within health organisations[6]; the stages are outlined below:

1. Determine the aim and scope of the priority setting exercise
2. Compile a programme budget
3. Form a marginal analysis[3] advisory panel
4. Determine locally relevant decision making criteria
5. Advisory panel to identify options in terms of:
    a. Areas for service growth
    b. Areas for resource release through producing same level of output but with less resources
    c. Areas for resource release through scaling back or stopping some services
6. Advisory panel to make recommendations in terms of:
    a. Funding growth areas with new resources
    b. Decisions to move resources from 5b to 5a
    c. Trade-off decisions to move resources from 5c to 5a
7. Validity checks with additional stakeholders and final decisions to inform budget planning services.

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[3] *Marginal analysis is concerned with how to best use small changes in resource allocation or use between two or more programmes rather than what the overall average significance of that small change would be. The margin can be thought of as the next unit of a good or the next unit of input. For example, if the marginal benefit of the next unit exceeds the marginal cost, then it should be considered a good use of additional resources. The aim is to make best use of the marginal benefits/costs across programmes. PBMA is described in greater detail by Mitton and Donaldson[6].*

Overview of methods used in the Modell Global Database of Constitutional Congenital Disorders (MGDB)

Introduction

This chapter summarises the methods used in the Modell Global Database of Constitutional Congenital Disorders (MGDB) which provides country-level epidemiological data for congenital disorders (Modell, 2012, unpublished). These methods were developed to respond to the scarcity of data in most countries, particularly those that are less developed. The initiative started from a database of haemoglobin disorders created for the WHO and has been extended to other conditions. The database has provided inputs for several reports including the March of Dimes 2006 report on Birth Defects and the 2010 round of the Global Burden of Disease study and is also a source of data for PHGDB – the database which underlies the HNA Toolkit.

The estimates containeded within MGDB, focus on those congenital disorders that manifest in childhood or adolescence, and cause early death or disability in the absence of interventions. The estimates cover conditions classified by ICD10 codes Q00-Q99: "congenital malformations, deformations and chromosomal abnormalities", which are collectively called congenital anomalies (Table 1)[4]. The complexity of the ICD classification was simplified in order to develop a systematic approach that is generally applicable for the whole range of congenital disorders, and to describe outcomes in terms that are readily understood by a multidisciplinary audience and are relevant for public health. This is achieved by:

Grouping disorders, as far as possible, by clinical outcomes rather than by precise ICD 10 diagnosis;

Including only severe cases for each diagnosis, i.e. those that cause death or disability (Table 1); and

Including minimum estimates in all cases. The estimates refer to the year 2010, although they can be updated to more recent years.

The possible outcomes of (severe) congenital anomalies (disorders) are summarised in Figure 1. In the absence of diagnosis and care, all congenital disorders lead to early death or lifelong disability. Some interventions before or during pregnancy can reduce affected birth prevalence. After birth, early diagnosis and treatment can lead to definitive cure for some congenital malformations. However many, such as chromosomal disorders and some severe congenital malformations (e.g. of the CNS), cannot be cured and require supportive care for improved survival and quality of life.

[4] Conditions known to be caused by single-gene mutations (for example haemoglobin disorders) and those caused exclusively by environmental factors (such as radiation) are excluded from this classification. The data for the haemoglobin disorders that are used in PHGDB are form the CHIME Haemoglobinopathies Almanac (http://www.ucl.ac.uk/CHIME).

Figure 1: Factors affecting the epidemiology and outcomes of congenital disorders

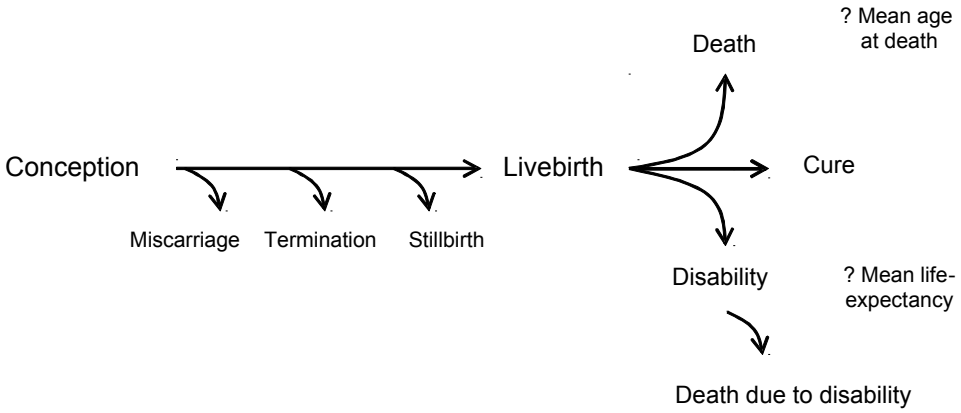

Table 1. Examples of pragmatic grouping of conditions according to broad outcome

Group of disorder		Conditions	Outcomes
Chromosomal disorders	Severe autosomal disorders	Down's syndrome, trisomies 13 & 18, unbalanced chromosomal rearrangements	Early death, long-term disability
	Sex chromosome disorders	Klinefelter's and Turner's syndromes	Lifelong problem: supportive care required
Neural tube defects		Anencephaly	Stillbirth, neonatal death
		Spina bifida and encephalocele	Infant death, long-term disability
Congenital heart disease	Early-onset CHD	Very severe CHD	Infant death, long-term disability
		Severe CHD	Cure, infant death, long-term disability
	Late-onset CHD	Bicuspid aortic valve	Valve failure after 45 yr of age

Steps for generating estimates

For each group of conditions, the following procedure was carried out:

A description of the condition, its consequences in the absence of care, and the history and effects of interventions

Development of modelled estimates for each condition following four sequential steps:

Step 1. Potential birth prevalence (in the absence of interventions)

Step 2. Effects of factors affecting birth prevalence (e.g. education and information on risk, changes in maternal age distribution, folic acid food fortification, prenatal diagnosis)

Step 3. Estimated birth prevalence (= 1 minus 2 above)

Step 4. Early mortality (neonatal, infant, under-5 mortality) and long-term survival, in different settings, calculated for the year 2010 and for the previous 50 years, and projected to 2050 using different assumptions.

Model outputs

The modelling procedure generates the following databases, which together comprise the MGDB.

A global database with estimates for 2010, by country and regions, of annual affected births, stillbirths, neonatal, infant and under-5 deaths for: Down's syndrome, other trisomies, unbalanced chromosomal rearrangements, Turner's syndrome, Kleinfelter's syndrome, neural tube defects, congenital heart disease, orofacial clefts, "other congenital malformations", single gene disorders and early-onset genetic risk factors (rhesus negativity and G6PD deficiency). In addition, work is underway on eight disorder-specific databases with estimates for 2010 of (a) numbers of living patients by 5 year age intervals, and (b) deaths by 5-year age intervals.

Birth prevalence rates are expressed both as affected births per 1,000 total births, and as affected live births per 1,000 total births. Separate estimates are given for stillbirths and terminations for fetal impairment. Mortality is expressed as the number of deaths in the total population (or by age group as appropriate) with rates expressed as the number of deaths per 1,000 live births (for neonatal, infant and under-5 mortality), adjusted for local mortality rates.

Data sources

Data are needed on birth prevalence and mortality for each diagnosis. However, even in high income countries, official registries rarely include data on births of infants with congenital disorders, and when they do there may be serious under-ascertainment. In lower income settings data is usually collected in hospitals at the time of birth. However, in the absence of advanced facilities such as routine fetal anomaly scanning and autopsy, only a minority of major congenital malformations (those that are obvious on external examination) are recognisable at this time, resulting in gross under-ascertainment of total prevalence.

High quality data on causes of death are usually available in high income countries, but mortality data provide very limited evidence on affected birth prevalence because, in general, when facilities for accurate recording of cause of death exist, diagnosis and care are also available and many congenital malformations are effectively repaired and leave the system. In lower income settings, particularly when autopsy is not available, serious under-ascertainment of deaths due to congenital disorders is inevitable.

Therefore reliable information can be obtained only from dedicated studies, usually conducted in higher income settings. Searches were carried out to identify these studies, which are described in the following sections.

Classical studies of the burden of congenital disorders

These included studies conducted after the second world war on the baseline birth prevalence of congenital and genetic disorders, in order to enable assessment of the likely effects of radiation exposure (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 1977, 1982). Table 2 lists the classical studies used and their scope. These studies are particularly valuable because data were obtained before interventions became available that can either reduce affected birth prevalence or increase ascertainment.

Table 2: Key classical studies of the birth prevalence of congenital disorders

Source	Chromosomal disorders	Congenital malformations	Single gene disorders
Stevenson 1959	+	+	+
Myrianthopoulos and Chung 1974		+	
Trimble and Doughty 1974	+	+	+
Ash, Vennart & Carter 1977	+	+	+
Hook and Hamerton 1977	+		
Czeizel and Sankaranarayanan 1984	+	+	
Baird et al. 1988	+	+	+

In addition, databases that cover most populations are available for ABO and rhesus blood groups (Mourant1954, Mollison et al. 1993), haemoglobin disorders (Livingstone 1985, Modell and Darlison 2008, www.modell-almanac.net/), G6PD deficiency (Livingstone 1985: WHO 1985c, Luzzatto and Mehta 1995) and customary consanguineous marriage (Murdock 1967, Bittles 1990, www.consang.net).

Congenital anomaly registries

Reliable observational data are usually available only for high or upper-middle income countries. Nevertheless, the available evidence indicates a broadly similar birth prevalence of congenital malformations world-wide, and therefore it is possible to extrapolate for lower income settings where no registries are available, though this should be done with caution.

The MGDB uses the following registries:

The British Columbia Registry (Baird et al.1988)

The Hungarian Congenital Malformation Registry (Czeizel and Sankaranarayanan 1984)

European Surveillance of Congenital Anomalies (EUROCAT, www.eurocat-network.eu, co-ordinator Helen Dolk). Most EUROCAT registries report affected live-births, stillbirths, and terminations of pregnancy following prenatal diagnosis, where this is legal. Detailed data are published on the web (Direct link to prevalence tables http://www.eurocat-network.eu/accessprevalencedata/prevalencetables). EUROCAT also produces a series of special reports and many published articles.

International Clearinghouse for Birth Defects Surveillance and Research Monitoring Systems (ICBDSR) (co-ordinator Pierpaolo Mastroiacovo). Annual reports are published on the web at www.icbdsr.org. ICBDSR registries aggregate live and still births. Not all report termination of pregnancies when this is legal. Data for 1985-90 and 2000-2005 were provided by Dr Mastroiacovo.

The Latin-American Collaborative Study of Congenital Malformations (ECLAMC) (co-ordinator Eduardo Castilla). Termination of pregnancy is illegal in most of South America. Data for 1993-98 are available in the World Atlas of Birth Defects (WHO 2003) and aggregated ECLAMC data are included in ICBDSR.

Literature search for epidemiological data

For chromosomal disorders, neural tube defects and congenital heart disease, a PubMed search was conducted with the aim of identifying papers relevant for birth prevalence in lower-income countries, and outcomes for affected children in different settings. The search identified 1,687 articles on chromosomal disorders, 709 on neural tube defects and 900 on congenital heart disease. Of these, 122, 146 and 151 respectively were selected for abstract or full text review. For orofacial clefts, data were extracted from a systematic literature

search including MEDLINE, EMBASE and OVID, which yielded 1,371 references, supplemented by extensive hand searching (Mossey and Little 2002).

Relevant websites were searched for data for specific conditions. For example, Wren and Sullivan 2001 give numbers of patients with a wide range of diagnoses seen at a regional specialist paediatric cardiology clinic, observed survival to 1 year, and predicted survival to 16 years by diagnosis. The data apply to 1985-1994. The data were used in the estimation of survival of individuals affected by this group of conditions.

Key articles with epidemiological data

The MGDB requires data on survival with near-universal access to diagnosis and best available care, and survival in the absence of diagnosis and care. When these two extremes are known survival can be estimated for any given population, using infant mortality as an indicator of access to care. Studies providing such data included the following:

Tennant et al (2010): Survival to 20 years of children born with congenital malformations in the Northern Region of the UK in 1985-2003.

Skaeraven et al (1999) and Lie et al (2001): 30-year survival and reproduction in Norway 1967-1982 for congenital anomalies

Czeizel and Sankaranarayanan (1984): survival to 1 year and 15 years, with estimates of later mortality. The data apply for Hungary 1970-81.

For outcomes in the absence of care, a range of early studies conducted in high income countries before the introduction of major interventions were used. Examples include Laurence and Tew (1971) for spina bifida, MacMahon et al. (1952) for congenital heart disease and Merrick (2001) for Down's syndrome. In the case of orofacial clefts, statistical data provided by the charity Smile Train (www.smiletrain.org.uk) were used to provide estimates of outcomes in the absence of diagnosis and care.

Other web-based sources

Global deployment of folic acid food fortification: The Flour Fortification Initiative (FFI), http://www.sph.emory.edu/wheatflour/countrydata.php

- Legality or otherwise of termination of pregnancy: United Nations. Abortion Policies: a global view (2002): http://www.un.org/esa/population/publications/abortion/profiles.htm Updated with http://www.un.org/esa/population/publications/2011abortion/2011wallchart.pdf

Wikipedia, Encyclopaedia Britannica.

Sources of demographic data

- The 2010 revision of the UN World Population Prospects (WPP) (http://esa.un.org/unpp) was used to obtain country specific demographic data by five year intervals. Data were obtained from the medium variant tables for: population number and age distribution, annual births, total fertility rate, infant and under-5 mortality and mean life expectancy, with supplementary data from the UN Demographic Yearbook (UNDY) series

  http://unstats.un.org/unsd/demographic/products/dyb/dyb2.htm

- The UNDY 1997 historical supplement provides demographic tables for the 50 years 1948 -1998.

http://unstats.un.org/unsd/demographic/products/dyb/dybhist.htm

Demographic sources identify countries/territories differently depending on their objectives. The UNDY classification, which uses an ISO-based classification, was used by MGDB. Estimates are made for each country for 1950, 1970, 1990, 2010, 2030 and 2050, based on WPP estimates for the preceding five-year interval. Gaps in WPP demographic data (for countries/territories with population less than 100,000) are filled using a near-neighbour approach.

All calculations are made for each individual country. The data are then aggregated and reported for 11 regions (Table 3), in which the countries are grouped according to geography and economic level of development. These groupings also apply for some cultural aspects such as legality of termination of pregnancy. The groupings are based on GBD, but these have been amalgamated into 11 regions as opposed to 21 regions used by GBD.

Table 3. Adaptation of GBD regional groupings for MGDB regions and countries

Countries	GBD region	Simplified Region used in MGDB
Angola, Central African Republic, Congo, Democratic Republic of the Congo, Equatorial Guinea, Gabon.	Sub-Saharan Africa Central	Sub-Saharan Africa
Burundi, Comoros, Djibouti, Eritrea, Ethiopia, Kenya, Madagascar, Malawi, Mozambique, Rwanda, Somalia, Sudan, Uganda, United Republic of Tanzania, Zambia.	Sub-Saharan Africa East	
Botswana, Lesotho, Namibia, South Africa, Swaziland, Zimbabwe.	Sub-Saharan Africa Southern	
Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Cote d'Ivoire, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Saint Helena, Sao Tome and Principe, Senegal, Sierra Leone, Togo.	Sub-Saharan Africa West	
Algeria, Egypt, Libyan Arab Jamahiriya, Morocco, Tunisia, Western Sahara.	North Africa	Middle East/North Africa/Central Asia
Bahrain, Iran (Islamic Republic of), Iraq, Jordan, Kuwait, Lebanon, Occupied Palestinian Territory, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Turkey, United Arab Emirates, Yemen.	Middle East	
Anguilla, Antigua and Barbuda, Aruba, Bahamas, Barbados, Belize, Bermuda, British Virgin Islands, Cayman Islands, Cuba, Dominica, Dominican Republic, French Guiana, Grenada, Guadeloupe, Guyana, Haiti, Jamaica, Martinique, Montserrat, Netherlands Antilles, Saint Kitts and Nevis, St. Lucia, St. Vincent, Suriname, Trinidad and Tobago, Turks and Caicos Islands.	Caribbean	South America
Bolivia, Ecuador, Peru.	Latin America, Andean	
Colombia, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Venezuela.	Latin America, Central	
Argentina, Chile, Falkland Islands (Malvinas), Uruguay.	Latin America, Southern	
Brazil, Paraguay.	Latin America, Tropical	
Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Mongolia, Tajikistan, Turkmenistan, Uzbekistan.	Asia, Central	East Asia
China, Democratic People's Republic of Korea,	Asia, East	
Afghanistan, Bangladesh, Bhutan, India, Nepal, Pakistan.	Asia, South	South Asia
Cambodia, Indonesia, Lao People's Democratic Republic, Malaysia, Maldives, Mauritius, Mayotte,	Asia, Southeast	Southeast Asia & Oceania

Myanmar, Philippines, Seychelles, Sri Lanka, Thailand, Timor Lester, Viet Nam.		
American Samoa, Cook Islands, Fiji, French Polynesia, Guam, Kiribati, Marshall Islands, Micronesia (Federated States of), Nauru, New Caledonia, Niue, Northern Mariana Islands, Palau, Papua New Guinea, Pitcairn, Samoa, Solomon Islands, Tokelau, Tonga, Tuvalu, Vanuatu, Wallis and Futuna Islands.	Oceania	
Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia and Montenegro, Slovakia, Slovenia, The Former Yugoslav Republic of Macedonia.	Europe, Central	East and Central Europe
Belarus, Estonia, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine.	Europe, Eastern	
Andorra, Austria, Belgium, Channel Islands, Cyprus, Denmark, Faeroe Islands, Finland, France, Germany, Gibraltar, Greece, Greenland, Holy See, Iceland, Ireland, Isle of Man, Israel, Italy, Liechtenstein, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, Saint Pierre et Miquelon, San Marino, Spain, Sweden, Switzerland, United Kingdom.	Europe, Western	High Income populations
Australia, New Zealand.	Australasia	
Canada, United States of America.	North America, High Income	
Brunei, Japan, Republic of Korea, Singapore	Asia Pacific, High Income	
Hong Kong, Taiwan	Asia East	

Description of model steps

Step 1. Establishing potential birth prevalence

Potential birth prevalence is the birth prevalence that would occur in the absence of any intervention.

Chromosomal anomalies

The birth prevalence of Down's syndrome (DS) is directly related to maternal age and was calculated using demographic data on maternal age distribution (see Step 2). Edwards and Patau syndromes are related to maternal age in the same way as Down syndrome (Hook 1992), and their joint live birth prevalence is approximately 15% of that of Down syndrome. This ratio is used to calculate their birth prevalence. The live birth prevalence rates for unbalanced chromosomal rearrangements (0.64/1000), Turner's syndrome (0.15/1000) and Klinefelter's syndrome (0.70/1000) are based on data from EUROCAT.

Forty per cent of infants with chromosomal disorders also have one or more congenital malformations, especially of the heart or gastro-intestinal tract. Both Czeizel and Sankaranarayanan (1984) and EUROCAT distinguish clearly between chromosomal and non-chromosomal congenital malformations. In the MGDB, malformations associated with chromosomal disorders are considered and counted as part of the chromosomal disorders.

Congenital malformations

The causes of congenital malformations are estimated to be multifactorial in 20-25% of cases; monogenic in 6-8%; environmental (e.g. maternal infections and illnesses, radiation and drugs including alcohol) in 6-8%; and chromosomal anomaly in 6-8% (EUROCAT Special Report 2004). There is no known cause in over 50% of cases. Monogenic-,

environmental-, and chromosome-associated malformations are excluded from the estimates for congenital malformations. A number of factors related to global variations in congenital malformations were taken into account based on evidence from the literature. For example the birth prevalence of neural tube defects varies with maternal folic acid intake (Berry et al 1999), and the prevalence of orofacial clefts varies with geographical situation and/or ethnic origin (Mossey and Little 2002). However, the general prevalence of congenital heart disease during pregnancy is considered to be similar world-wide (Hoffman 1995). The birth prevalence of neural tube defects is related to maternal vitamin intake. There is evidence that the birth prevalence of some other severe congenital malformations, including congenital heart defects (Botto et al 2006) is linked to maternal folic acid status, but this was not considered in making the present estimates.

In common with other outcome studies (e.g. Czeizel and Sankaranarayanan 1984, Tennant et al. 2010) the MGDB reports in terms of affected individuals. However most congenital anomaly registries report in terms of malformations. Since several malformations can co-exist in one individual, uncritical use of registry data could lead to double-counting. To obtain rates for total isolated malformations, average total birth prevalence should be reduced by 13.2%, average termination rate should be reduced by 31%, and average fetal death rate should be reduced by 33.5%. However it is also possible to make group-specific estimates for associations. MGDB uses published data for isolated neural tube defects (Stoll et al. 2011), oro-facial clefts (EUROCAT Special Report 2000) and congenital heart disease (EUROCAT Special report 2009). The proportion of associations for other types of malformations was based on Rittler et al. 2008 and Garne et al. 2011.

Overlap between different categories of congenital malformation, and data duplication

Because some affected individuals have multiple malformations, estimates of the prevalence of malformations will be higher than estimates of prevalence of affected infants. For example EUROCAT data show the former to be 13.7% higher than the number of affected infants. The model deals with duplications in the following way: in MGDB, country rates for non-chromosomal malformations (when available) are entered. Total rates for isolated malformations are calculated using EUROCAT rates for neural tube defects, oro-facial clefts and congenital heart disease. Rates for termination and fetal death for these conditions are adjusted using. EUROCAT average rates for isolated conditions in those countries without epidemiological data.

- Chromosomal disorders – associated malformations are considered as part of the chromosomal syndrome.
- Neural tube defects – isolated cases only. Those associated with other defects and chromosomal disorders are not included.
- Congenital heart disease –isolated cases only. Those associated with chromosomal anomalies and other malformations are not included in this category.
- Orofacial clefts – isolated cases only. Those associated with chromosomal anomalies and other malformations are not included in this category.
- All other malformation categories – non-chromosomal cases only. The full procedure described below is followed, but 20% is removed from the final estimates.
- Single gene disorder – include haemoglobin disorders and all consanguinity associated disorders including congenital malformations.

Stillbirths

The distinction between stillbirth and neonatal death is important; however, the borderline between these can be quite blurred. Gestational age criteria for stillbirth (versus miscarriage)

differ by country, with cut-offs ranging from 20 to 28 weeks. EUROCAT registries report in their own country's terms, but registration of "fetal deaths" after 20 weeks' gestation is encouraged.

Table 4 shows data on the proportion of stillbirths in relation to live births adopted in the estimates and based on EUROCAT data. These were used to derive estimates for stillbirths from live births.

Table 4. Approximate stillbirth rate associated with the selected disorders

Anomaly	**Stillbirths as % of live births**
Chromosomal Total	8.6
Down's syndrome	4.0
Patau's syndrome/trisomy 13	19.9
Edwards' syndrome/trisomy 18	40.3
Turner's syndrome	27.0
Klinefelter's syndrome	2.0
All non-chromosomal total	2.33
Neural tube defects	18.4
Congenital heart disease	1.8

Step 2. Establishing effects of factors that affect birth prevalence

The effects of the following interventions are taken into account in the MGDB.

Changes in maternal age distribution

These changes have a profound effect on birth prevalence of chromosomal disorders. Based on the UNDY series, including the UNDY historical supplement, the following formula can be derived to estimate live births due to Down's syndrome based on the proportion of mothers over 35 years of age (with no termination of pregnancy).

Down syndrome potential live births /1,000 = 0.834 + 0.067 x (% mothers 35plus) (+/- 4.2%)

The birth prevalence of Edwards' and Patau's together can be estimated as 15% of DS live birth prevalence.

Folic acid fortification

Multivitamin and folic acid supplementation and fortification of foodstuffs with folic acid affect the birth prevalence of neural tube defects, and to lesser extent of orofacial clefts. The model considers the observed effect on NTDs, and estimates the effect on orofacial clefts and congenital heart disease as 25% of per cent reduction in NTDs. Since the coverage of supplementation starting before pregnancy cannot be estimated, and is expected to be low in most low and middle income countries, the model only takes into account the effect of food fortification; this is based on the country-estimated coverage of folic acid fortification and the effectiveness of folic acid, based on its concentration in staple food.

- Information on national policies and coverage of folic acid fortification is obtained from the flour fortification initiative (FFI) website:

  http://www.sph.emory.edu/wheatflour/countrydata.php.

For countries with folic acid food fortification and observational data, the observed percentage fall and post-fortification birth prevalence are used. For countries with mandatory fortification but no observational data on effects, the expected percentage fall in neural tube defect birth prevalence is calculated using FFI data on additional micrograms of folic acid per

100g of flour, and predictions of effect based on baseline NTD prevalence and dose of folic acid in the fortified food. The relationship is based on Wald et al (2001). This relationship is illustrated in Table 5, and reflects quite conservative estimates of effects of folic acid fortification.

Table 5. Estimated fall in NTD prevalence, in relation to dose and pre-fortification prevalence (based of Wald et al. 2001)

Folic acid ug / 100g flour	Extrapolated predicted % reduction in NTD			
	Baseline NTD 2.5 /1000	Baseline NTD 1.8 /1000	Baseline NTD 1.2 /1000	Baseline NTD 1.0 /1000
140	49.5	28.9	20.0	15.7
200	62.6	40.0	27.8	22.6
350	75.1	50.0	37.3	30.1

Termination of pregnancy following prenatal diagnosis

Data on termination for fetal abnormality are available from registers that participate in EUROCAT and ICBDSR. These are used where available, with adjustments for under-ascertainment and access to care made as appropriate. Near-neighbour assumptions are made for 58 small countries without participating registers, out of 88 countries where termination of pregnancy is permitted. However, important information gaps remain for many countries where prenatal diagnosis is available. For these countries, the proportion of affected pregnancies terminated is estimated on the basis of legality or otherwise of abortion for fetal impairment, the estimated proportion of women with access to specialist services, and EUROCAT diagnosis-specific average termination rates.

For countries where termination for fetal abnormalities is illegal (96 countries at the time of writing), it is assumed that no terminations for fetal abnormality take place, although some are almost certainly done for malformations.

Step 3. Establishing birth prevalence (total and live birth prevalence)

The estimated (total) birth prevalence is derived from potential births minus births avoided due to interventions before pregnancy, such as folic acid fortification of foods and administration of anti-D to rhesus negative women after delivery, or to prenatal diagnosis leading to termination of pregnancy, estimated as above. For some conditions, no terminations are considered, e.g. uncomplicated orofacial clefts.

The estimated live birth prevalence is calculated by subtracting estimated stillbirth prevalence from actual total birth prevalence.

Step 4. Calculating mortality due to congenital disorders

Two types of survival curves are required for each group of condition in high- and lower-income settings.

Prospective survival curves describe survival/mortality at the present time (corresponding to 2010). They are used to calculate current annual deaths due to the condition(s) concerned, and to project likely deaths in the future. They are based on the most recent observations available.

Potential early deaths due to congenital malformations and potential survivors past age 5, are calculated from annual affected live births, the high income and no-care survival curves, and estimated access. However affected children can die of other causes. To adjust for background early mortality, the corresponding proportions of local early mortality rates are deducted to obtain *attributable* early mortality rates, and actual survivors past age 5.

Prospective survival curves, high income settings

Since many congenital disorders cause early death, mortality data up to five years of age are available for most of the conditions under consideration. These are complemented by information from valuable disorder-specific articles on long-term survival.

Since many of the interventions responsible for improved survival were introduced in the past 30-40 years, there is very little observational data on survival beyond 30-35 years of age. These rates are estimated by extrapolating available observed mortality in the oldest 5-year age groups to 70-80 years of age. Mean age at death can also be calculated when long-term survival curves are available.

Survival in lower-income settings

The sparse information in the literature on survival in these settings includes reports such as Venter et al. 1995 and Delport et al. 1995 for rural Africa, and Castilla et al. 1998 for Latin America. These are used as appropriate. They have been complemented by expert opinion: Dr Christopher Wren provided diagnosis-specific estimates of outcomes for congenital heart disease in the absence of intervention; Christianson and Modell estimated outcomes for all other malformations listed by Czeizel and Sankaranarayanan (1984) in the absence of intervention. EUROCAT's list of disorders includes information on conditions requiring operation: for these diagnoses early death is assumed for most unoperated babies. Smile Train, a large charity that provides repair for oro-facial clefts in a range of countries provided data on numbers and age at operation from which mortality rates could be estimated.

However, in many cases the model uses data from reports for high income countries from the 1950s and 1960s, before modern therapeutic interventions were available. Such reports can be used to estimate best possible survival in settings where no care is available.

Combining these data enabled survival curves to be developed for different settings. For example, Figure 2 uses the example of Down's syndrome to estimate survival in those affected in a range of settings.

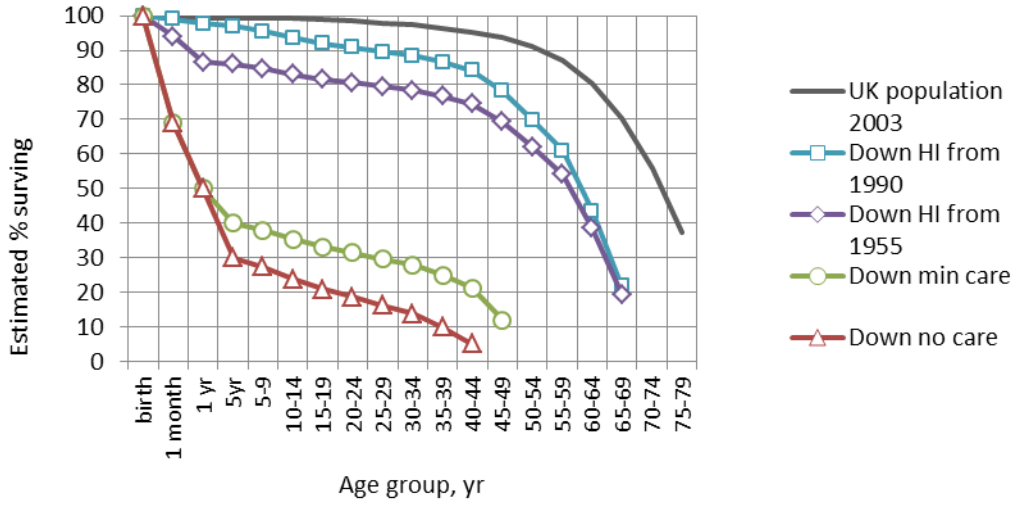

Figure 2: Prospective survival curves for people born with Down's syndrome, in different settings.

Generating country-specific survival curves

As explained above, survival curves can be generated for the two extremes, namely best possible care (defined as the level of care available in a typical high income country), and

absence of diagnosis and care. These curves can be applied for the highest and lowest income countries respectively, and can also be used to generate hypothetical survival curves for countries at intermediate levels of development.

The estimates for extreme situations can be used to derive estimates for specific countries, based on estimates of the proportion of the population covered by health services. These can be obtained by using simple, available indicators, such as neonatal or infant mortality. The WHO Child Health Epidemiology Reference Group (CHERG) has identified five neonatal mortality groups as indicators of service quality. Infant mortality is the preferred proxy indicator of access in the MGDB because the data are readily available at the sub-national as well as national level (WPP and UNDY do not include neonatal mortality).

IMR-based estimates of access were developed in two steps. First, infant mortality groups corresponding to CHERG neonatal mortality groups were obtained by relating neonatal and infant mortality rates for 2005 (Fig 3). Table 6 shows the "corresponding infant mortality ranges". Since the development of services is exponential rather than discontinuous, a continuous curve was fitted to the stepped curve, using a function based on the cumulative Beta distribution function to achieve a more refined estimate of access. The continuous proportion with access to services (p) is predicted from the infant mortality rate using a formula. (1-BETADIST(LN(IMR-10),2.5,5.5,0,LN(1000)))

Table 6. Neonatal mortality groups used by CHERG

Group No	Mortality level	Estimated services for congenital disorders	CHERG Neonatal mortality ranges	Estimated % with access to care	Corresponding infant mortality ranges	Estimated % with access to care
1	Very low	Optimal diagnosis and care	≤5	Nearly 100%	0-9	Nearly 100%
2	Low	Evolving diagnosis and care	6 – 15	99-(IMR-6) x 5.67	10-24	99-(IMR-6) x 5.67
3	Moderate	Diagnosis and care for some	16 – 30	15%	25-54	15%
4	High	Diagnosis and care for small minority	31 – 45	5%	55-99	5%
5	Very high	No diagnosis or care	> 45	None	100 plus	None

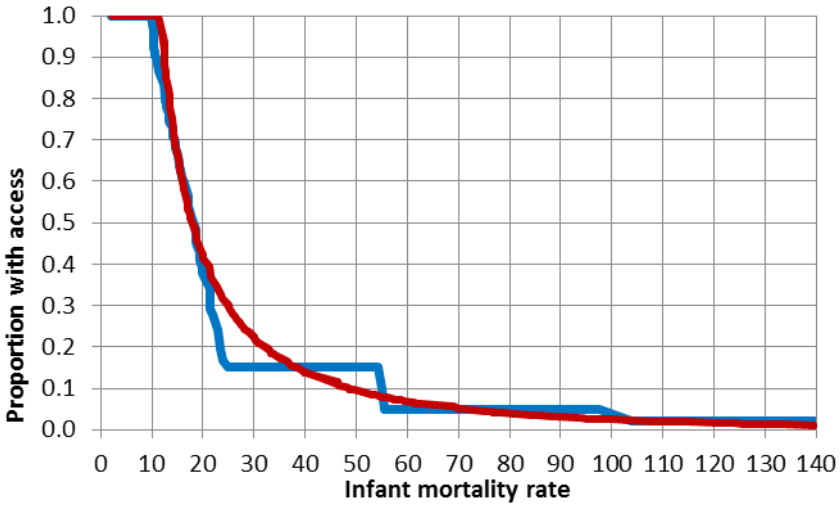

Figure 3. Comparison of IMR-based estimates of access to specialist services in 2005 for 196 countries. The stepped (blue) curve shows access calculated using CHERG-based IMR groups. The continuous curve shows the result of applying Dr Gibbons' equation to the infant mortality data.

Describing mortality

The number of deaths due to a disorder may be different from the number of deaths of people with the disorder. In allocating mortality to a particular disorder, background deaths (that would have occurred if affected children had been born without the disorder) have been subtracted from total deaths of those with the disorder. This means the estimates are for *excess deaths due to each disorder*.

Limitations of the model

Scarcity of data is the main limitation for building reliable estimates of disease burden. While this limitation justifies the development of the mathematical model, it must be kept in mind when data are interpreted.

Data, when available, are as good as the studies or registries generating them. For example, ascertainment is the critical problem for registries. The greatest risk is of under-ascertainment, though there may also be over-ascertainment e.g. due to referral bias. There are considerable differences between registries in the upper age limit for registration: those with an upper limit of 1 week (hospital discharge) inevitably miss many less obvious cases, and those with an upper limit of one year cannot include later-presenting cases. Average prevalence figures from umbrella registries have often been taken to represent global baseline prevalences. In general, these average prevalences should be viewed as minimum prevalences.

The lack of data for many places means that extrapolation is necessary. Thus when no or only limited data are available for a country, estimates are made using available data.

When multiple sources of data are available, a judgement needs to be made as to what weight should be given to different sources; this may increase uncertainty. However, whenever appropriate, the model errs on the side of under-estimation of disease burden; thus in general minimum estimates consistent with the data are used throughout the exercise. An exception includes the assumption of no termination of pregnancy in places where this is illegal, which tends to over-estimate birth prevalence. This may result in an over-estimation of mortality, which results in an under-estimation in survivors and consequently on the number of survivors with a disability. In addition, the effects of folic acid in preventing congenital disorders might have been under-estimated, leading to an over-estimation of birth prevalence. This may have arisen due to a combination of factors including: possible over-estimation of coverage of folic acid fortification in some places; and not accounting for effects of pill supplementation.

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Glossary

This section contains some terms which are commonly used within various documents of the Toolkit, however, it is not a comprehensive list.

Aetiology	Either study of the cause of disease or assignment of disease cause
Allele	Variant forms of the same gene.
Audit	An evaluation of a person, organization, system, process, enterprise, project or product
Autoimmune/autoimmunity	Immune response against an organisms own cells due to a failure to recognise substances normally present in the body.
Autosome/autosomal	Refers to the chromosomes that are not concerned with sex determination. Humans have 22 pairs of autosomes, plus two sex chromosomes (X and Y).
Birth defect	The way we use it, the term 'birth defect' is synonymous with the terms 'congenital anomaly' or 'congenital disorder'. See 'congenital disorder'.
Birth prevalence	The number of persons with a disease at birth.
Body mass index (BMI)	The body mass index (BMI) is a person's weight in kilograms (kg) divided by their height in meters (m) squared. Used as a determinant of obesity.
Carrier	Usually refers to an individual who is heterozygous for a recessive, disease-causing allele. A carrier of such an allele usually shows no symptoms of the disease but can pass the mutant allele on to his or her children. If both parents are carriers, there is a one in four chance (25%) that each child will be homozygous for that allele and will therefore be affected by the disease.
Cascade screening/testing	Offering carrier testing to the relatives of a person who has, or carries, an inherited disorder. This is usually done in collaboration with the presenting patient or (in the case of a child) with their parents. The first step is to take a genetic family history in order to identify relatives who may be carriers. These may then be contacted, informed of their risk and offered testing.
Cause-specific ascertainment rate	The proportion of deaths registered as due to the specific cause out of the total number of deaths due to the specific cause.

Congenital anomaly	The way we use it, the term 'congenital anomaly' is synonymous with the terms 'birth defect' or 'congenital disorder'. See 'congenital disorder'.
Congenital disorder	We define the term congenital disorder as any abnormality affecting body structure or function that is present from birth, whether or not it is manifested in early life.
Cost-effectiveness	The extent to which an activity is thought to be as valuable as it is expensive. Cost-effectiveness analysis is a form of economic evaluation.
Dominant allele/inheritance	Inheritance of a mutation from one parent only (or arising anew during egg or sperm formation) can be sufficient for the person to be affected.
Ectopic	An ectopic pregnancy is one located outside the inner lining of the womb.
Effectiveness	A measure of the extent to which a specific intervention or service fulfils its objectives.
Efficacy	The extent to which a specific intervention produces a beneficial result under ideal conditions. Ideally this is based on a randomised controlled trial.
Efficiency	A developing fertilised egg up to the stage that the main organ systems have been laid down, i.e. the 8th week from conception (= 10 weeks from the last menstrual period).
Embryo	A developing fertilised egg up to the stage that the main organ systems have been laid down.
Endemic	Constant presence within a given geographic area or population group.
Epidemic	Occurrence in excess of normal expectancy of cases of health-related events in a common region.
Etiology	see aetiology
Eugenics	Selective breeding to improve the genetic constitution.
False negative	Negative test result in a person who possesses the attribute for which the test is conducted.
False positive	Positive test result in a person who does not possess the attribute for which the test is conducted.
Fetus	An unborn human more than 8 weeks after conception

Gene	A part of the DNA molecule of a chromosome which encodes (directs the synthesis of) a protein.
Gestation	Period of time from conception to birth.
Haemolysis	Breakdown of red blood cells.
Haemoglobin/hemoglobin	Haemoglobin is an iron-transporting protein located in red blood cells.
Health needs assessment (HNA)	A health needs assessment (HNA) is a systematic method aimed at identifying unmet health needs in a population and making changes in response to address those needs. Health care need relates to the ability to benefit from (health care) interventions or services. Health needs also include the ability to benefit from changes to the frequency and distribution of risk factors, and of social and environmental factors that influence health, e.g., socioeconomic status, education, diet, employment and behaviour. Need relates to the occurrence and severity of the problem under consideration, the effectiveness and cost-effectiveness of interventions addressing the problem, and the availability of and access to services and interventions by those who need them. Identifying (and addressing) inequalities in determinants of health and services are important components of the HNA.
Heterozygosity/heterozygous	An individual who carriers two different alleles of a particular gene. An individual who carries two different mutant alleles in the same gene is said to be a compound heterozygote.
Homozygosity/homozygous	An individual who has two identical copies of a particular gene.
Iron chelation therapy	Treatment for removing iron from the body. This is usually for people who have regular blood transfusions such as those with sickle cell disease. The iron produced as a result of breakdown of transfused red blood cells cannot be excreted and must be removed before levels become harmful.
Mutagen	Something capable of causing a gene change e.g. radiation.
Neonatal	Term relating to a newborn child, especially used in the first week of life and up to four weeks or a month old. Often used interchangeably with newborn.
Population prevalence	The number of persons with a disease in a given population

Quality adjusted life years (QALY)	A year of life adjusted for its quality or its value. A year in perfect health is considered equal to 1.0 QALY. The value of a year in ill health would be discounted. For example, a year bedridden might have a value equal to 0.5 QALY.
Recessive allele/inheritance	A mutation has to be inherited from both parents in order for a person to be affected. Such parents are often unaffected carriers because they only have a single copy of the mutant gene.
Risk factors	A range of factors, from the individual level to wider societal factors, that affect the occurrence (prevalence, incidence) and severity of congenital disorders.
Stillbirth/stillborn	Delivery or birth of a fetus that has died before birth.
Sequelae	Any abnormality following or resulting from a disease or injury or Treatment.
Total fertility rate (TFR)	TFR is a synthetic indicator of the level of childbearing in a population at a given point in time. It is the number of children that a hypothetical woman would have if she experienced the age-specific fertility rates in that population at that time.