Training in Reproductive Health Research
Geneva 2005

Systematic review on the prevalence and epidemiology of infertility 1999-2004 (Study protocol)

Tracy Parnell, MD
Director, Phase III
Rural and Community Health
University of British Columbia School of Medicine
Canada

Table of contents

1. Introduction

The distress and personal devastation experienced by couples suffering infertility has been documented since the beginning of recorded time in cultures throughout the world. Recent data gathered by the World Health Organization (WHO) through Demographic and Health Surveys in developing countries estimates that 186 million married women (excluding China) were infertile in the year 2002. [1] Previous estimates had the number afflicted with infertility at 60 –80 million.[2] This represents a substantial increase in the absolute number of people with infertility. Modern medicine has made several advances in the diagnosis, treatment and prevention of infertility over the last fifty years; however, the full scale of the problem is not known. Accurate information on the prevalence and contributing causes of infertility is crucial to public health planning, prioritisation and forecasting.

The WHO defines infertility as two years of exposure to pregnancy without conceiving.[3] Other medical and demographic definitions also exist. Defining etiologic causes is complicated by numerous definitions and diagnostic criteria used. For the purposes of public health planning, accurate assessment of the prevalence of various infertility etiologies is required in order to plan appropriate strategies for prevention, treatment and management of health and socio-economic consequences. The gap that currently exists between epidemiologic knowledge, program planning and research could be greatly reduced if an accurate synthesis of data was available to planners and policy makers, potentially resulting in more accurate needs assessments and more efficient resource allocation.

Infertility is an issue of concern to public health professionals and public policy makers for a number of reasons. Infertility is a medical condition that not only has health implications for those involved, but is a condition linked with individual human rights. The United Nations has declared that a woman has the right to choose the number of children she wishes and when she wishes to have them.[4] Arguments against dealing with infertility in favor of attempts to reduce overall fertility rates and control population growth [5], seriously violate this basic fundamental right, and are not well founded scientifically.[6] As well, this is a serious violation of the UN declaration on the rights of

individuals to form families of their choosing[7] and would be akin to suggesting the stopping of all STI/HIV programs in that this intervention may increase the fertility rate. Most developing countries have a higher prevalence of infertility than is found in the developed world.[8] Women too often carry the burden of the disease, as it is presumed in many cultures that the female partner in a relationship afflicted by infertility is the source of the problem.[9] This may lead to increased violence towards women, divorce and economic destitution. [10] Changes in sexual behaviour, with multiple partner exposure over time either through divorce, polygamy or other sexual partners, may result in an increased risk of exposure to HIV in infertile women in some situations.[11] To have a true picture of this problem it will be necessary to synthesize information currently gathered at an institutional level in many countries.

Research conducted over the last decade or so, has begun to recognize that infertility itself may be a contributing factor to maternal and neonatal morbidity and mortality.[12] [13] The exact aetiology of this phenomenon is not known, though it is hypothesized that untreated conditions that resulted in the infertility may also lead to subsequent morbidity.[14] Infertility caused by polycystic ovarian syndrome may also increase the risk of women subsequently developing serious health problems including endometrial cancer, high blood pressure, diabetes and heart disease. [15] [16] Again the exact mechanism is not understood, but the resulting complications may have a markedly adverse affect on the person afflicted as well as on the health care system. These issues and their impact on individuals and on the delivery of healthcare are obviously a high priority for health planners, policy makers, clinicians and researchers.

Infertility appears to be a widespread condition that has profound socio-economic and health consequences on the individual and society.

In order to address these pressing issues, a comprehensive review and critical appraisal of the literature is proposed, much of which is generated at a local or regional level. It is proposed to utilize methodology successfully developed and used by the WHO for the systematic review of maternal morbidity and mortality . [17] This approach applies to descriptive epidemiology the concept of systematic review of effectiveness in evaluating and synthesizing research.

2. Objectives of the review

The review aims to provide recent epidemiological evidence to assess the prevalence of infertility and its etiologic factors. It hopes to identify etiologic causes of high priority to support the implementation of programmes aimed at preventing infertility or minimizing the socio-cultural and health impact on individuals and the healthcare system. The main objectives of this review are:

- To provide a comprehensive, standardised and reliable tabulation of available data on prevalences of infertility and its causes,
- To provide a comprehensive, standardised and reliable tabulation of available data on the burden and share of the different infertility aetiologies,
- To provide regional or national data for comparison to the Maternal Morbidity and Mortality Data for evaluation of the possible contribution of infertility diagnosis on rates of morbidity and subsequent mortality by identified causes.
- To establish the basis to estimate the proportion of infertile couples that could be averted by eliminating or reducing the prevalence of certain morbidities.

Secondary outcomes:

- To identify a standard set of definitions and diagnostic criteria for infertility and infertility etiologies.
- To identify what percentage of studies selected also address the impact of infertility on the individual from the perspective of sociocultural, economic & health factors (burden of disease)
- To evaluate the usefulness and effectiveness of each source of information (e.g. Medline, LILACS, Ministry of Health, Registries, personal contact) in retrieving relevant citations in this field.

As well, in the future it is hoped to evaluate the methodology, particularly the use of dispersed reviewers and the on-line data extraction and collection system.

3. Type of study designs

3.1 Study designs for the overall prevalence of infertility

For infertility prevalence any study design providing prevalence or incidence rates for any definition of infertility in any population will be included for assessment. Those

include cross-sectional, cohort, clinical trials, international/national/regional registries, statistics and surveys of incidence/prevalence. Studies, which involve a calculated estimate or a modelled calculation of infertility prevalence, will be reviewed, though not necessarily included in the data analysis.

3.2 Study designs for the prevalence of etiologic causes of infertility

For etiology prevalence any study design providing prevalence or incidence rates for any defined cause or any definition of infertility in any population will be included for assessment. Those include cross-sectional, cohort, clinical trials, registry statistics, case-control studies and surveys of incidence/prevalence. In studies reporting the results of an intervention on a given aetiology, the control arm will be used for the review with respect to determining prevalence. Infertility for this purpose could be diagnosed by clinical, laboratory or diagnostic examination or be self-reported. Any comments on long-term morbidity, psychosocial impact or sequelae will be noted.

Case control studies will be reviewed; however, their contribution will only be included if there is data that can be used to determine the prevalence of certain causative etiologies of infertility.

Contact will be made with specialized infertility clinics to determine if they formally collect statistics on the prevalence of diagnostic etiologies of patients presenting with infertility. If this data, however, has already been contributed to any registry system, the data will be excluded.

3.3 Type of participants

Heterosexual couples of normal reproductive age (females menarche to menopause, males over age 14) that have had or who have infertility, irrespective of how this is defined. Data that includes figures for same-sex couples, single women who wish to conceive, and couples outside the normal reproductive age range will be reviewed; however, data that deals exclusively with these groups will not be included in the analysis.

3.4 Types of outcomes

3.4.1 Prevalence of infertility

It is expected that the results for the prevalence of infertility will be expressed as the number of couples per 100, 000 according to geographically defined areas or countries. The results will also be used to formulate a global estimate of the true prevalence of infertility (aggregate assessment), based on applying the prevalence calculation (percentage) to the relevant population of couples in the reproductive age.

3.4.2 Prevalence of etiologic causes of infertility

The International Classification of Disease, 10th revision (ICD-10)[18] defines infertility broadly as the inability to achieve a pregnancy or as sterility, excluding the condition of relative infertility, which is a term used for women who habitually abort (section N96). The specific ICD 10 coding for infertility is included under section N97 (Female infertility) and N 46 (Male infertility); however, there are a number of other conditions in the ICD 10 that may well represent the etiologic causes of infertility. These are listed in table 1. Although the reviewers will attempt to use these definitions when coding the etiologic cause of infertility, a high degree of heterogeneity is expected.

It is expected that significant variability will exist in not only the definitions of various etiologic causes of infertility, but also in the diagnostic criteria and evaluation processes used to determine them. This will likely have an impact on the ability to pool and compare results. However, outcome analysis will attempt to stratify the results according to simplified pooled categories:

1.0 Female only infertility

- 1.1.0 structural abnormalities female
- 1.2.0 endocrine abnormalities female
- 1.3.0 unexplained infertility female

2.0 Male only infertility

- 2.1.0 male factor

3.0 Multi-factorial infertility

- 3.1.0 structural abnormalities female **plus** endocrine abnormalities female
- 3.2.0 structural abnormalities female **plus** male factor
- 3.3.0 endocrine abnormalities female **plus** male factor

3.4.0 structural abnormalities female **plus** endocrine abnormalities female **plu**s male factor

4.0 other

5.0 unable to determine from data

More detailed descriptions of the aetiology (ICD 10 diagnoses or others identified in the study) will be analysed independently where appropriate. It is hoped to categorise each of these detailed diagnoses into the simplified categories listed above (i.e. PCOS may be 1.2.1 under endocrine abnormalities female).

Diagnostic criteria and evaluation procedures used in the individual studies will be extracted and analysed. Variability or inconsistency of definition and diagnostic criteria will be assessed and a stratified analysis performed where feasible. Stratified pooled analysis of data of specific aetiologies of interest will be performed (i.e. PCOS) if possible. This data will be analysed and applied as a projected proportion to the population of couples of reproductive age, on a global and geographically determined basis.

3.4.3 Other outcome measures

Socio-cultural, economic & health factors that contribute to the burden of disease on an individual and system-wide basis are secondary measures in this process. The percentage of studies that quantify these variables will be calculated. These studies will be identified as possibly forming the foundation for future studies looking in greater depth at these variables.

4. Methods of the review

4.1 Reviewer selection and training

Much about infertility diagnosis is determined at the level of the institution or clinic. In order to facilitate the process of acquiring all possible references, it is proposed to use reviewers with local knowledge expertise. In order to accomplish this and to ensure reviewers have some understanding of how to perform a systematic review, previous students who have undergone the WHO training in Research Methodology and Reproductive Health will be asked to participate as geographically defined reviewers. They will be responsible for accessing data and references in the regional languages and from non-published or non-traditional resources, including government, university

centers, infertility treatment clinics and registries, where applicable. If necessary, they will be provided with resources to enable them to participate in the review, thus building local capacity and collaborative ability to conduct research in keeping with the GFMER / WHO mandate.[19] This will also provide additional practical skills building upon the research fundamentals learned during the Research Methodology Course, again providing and enhancing national expertise.

The efforts of the dispersed reviewers will be coordinated by a small central team, which will seek to be available to answer questions and direct the review effort. The training for the review will take place through small regional meetings, with follow up provided through free teleconferencing or videoconferencing resources. There will be a conference mid-way through the review in order to facilitate discussion on relevant issues and to consider other applications for the research structure in place with this model.

4.2 On-line data extraction and collaboration

Using the proposed model for dispersion of the reviewers, it will be necessary to have a system to permit easy integration of data collected from various sources. It is proposed to utilize a secure online database collection system piloted through the GFMER website. This site and existing personnel and support infrastructure are already in place and familiar to many of the reviewers.

The benefit of the online site is that real time statistics are possible, as is further analysis and input of additional material in the future. This system is also to decrease data entry errors by having limited option choices (i.e. ‘yes’ or ‘no’) and by virtue of eliminating illegible writing that is difficult to interpret with a scanner. The system also enables administrative review of data entry to ensure compliance with data entry guidelines prior to final submission and inclusion of extraction form.

This model should facilitate the collaborative effort put forth by the reviewers and enable individual reviewers to propose and participate in additional research at a regional or more global level. The online structure and instant teleconferencing capacity via Skype or other GFMER facilitated resources will enable researchers to interact with one another in real-time with minimal cost.

4.3 Data extraction

All studies and data identified with the search strategy will undergo an initial screening review for assessment of inclusion or exclusion criteria. This initial screening will be based on a review of the titles and abstracts (when these are available). Data from non-traditional or registry sources will be screened with a form to be designed specifically for that purpose. Irrelevant records will be discarded and full text of the remaining will be obtained. Full text of studies whose available citations did not provide sufficient information to decide will also be obtained.

Each entry that meets the initial screening criteria will be reviewed as full text entry. A special screening form for each full-text evaluated report will be developed. Additional inclusion and exclusion criteria will determine whether or not the report will subsequently undergo full analysis. Those reports excluded will be compiled into an 'excluded' database and the reason for their exclusion noted. All criteria will be reviewed for each entry and all exclusion criteria documented in the online form.

For those studies meeting all the criteria for inclusion, data extraction will occur. Reviewers will enter data from the study directly into the online system. Following the model of the Maternal Morbidity and Mortality Study, the data extraction forms will assess several study criteria including: 1) characteristics of the study, including study type, design, patient population, location etc.,.; /2) prevalence /incidence of infertility; 3) the prevalence / incidence of specific infertility etiologies; 3) quality assessment of reports. The on-line data extraction form will have a built-in capacity to provide a description and definition for each item. Questions regarding other items can also be sent to the administrator via the website. The screening and data extraction form will be tested prior to full implementation.

4.4 Management of studies and data extraction

All citations identified for the study will be stored in the Reference manager® bibliographic software, available through the research area of the website. This software will be used to keep track of all citations, making it possible to identify and remove duplicates. It also has the capacity for direct entry of electronic searches. Other entries retrieved through non – electronic sources will be entered manually.

Reports retrieved from other sources (e.g. hand searching, personal contract) will be entered in Reference Manager® manually after the electronic searches. Each entry will be assigned a unique identification number.

As previously noted, full text reports will undergo an additional screening according to the screening assessment form. It is proposed to save all test reports in an electronic form, either by accessing and centrally storing it in that format or by storing it as an image file via electronic scanning (when not prohibited by law). This will facilitate any subsequent retrieval of the report, which will be stored by title, author, keywords and study type, if feasible.

Following the citation entry and electronic storage of the report, the identified reviewer will extract the data using a pilot-tested data-extraction form. When difficulties arise from this process the reviewer may discuss this either via email, of through identifying another reviewer who is online at that time. This consultation and its outcome will be noted on a special section of each data entry form. The questions may also be directed to the coordinating team member responsible. If the report is missing information or the reviewer has questions that need to be clarified, attempts will be made to contact the study authors. These attempts and their outcome will be noted on the online form.

In order to examine the usefulness and effectiveness of each source of information, each record in Reference Manager, the electronic text storage and the data extraction form will contain a field indicating such a source. The assessment of report source for each stage of the process will enable some calculation as to the most used source of information (i.e. 60% of Medline sources were screened as text, 20% were analyzed further). Further, by calculating the percentage contribution of each source type to the final data it may be possible to gauge how useful the various sources were. This may provide guidance to researches designing related search strategies in the future. For studies identified by more than one source, all sources that identified such a study will be kept.

4.5 Pilot project

Using the Maternal Morbidity and Mortality Study as a model, it is proposed to test the data extraction forms and methods for the initial study year of 1999. Studies in this year will be identified as per the initial screening form. A random sampling of these

will be additionally screened by two independent reviewers from the coordinating team. A third reviewer will resolve difficulties or any questions that arise. It is hoped that this will identify defects or inconsistencies in the data-extraction form. The form and three sample reports will be circulated to reviewers for comments. The final version of the form incorporating reviewers' suggestions and corrections of problems will be prepared after the pilot test.

4.6 Critical appraisal of studies

Studies included in the data extraction phase will be assessed as to the quality of the study. The characteristics of each study will also be appraised, allowing for some assessment of the heterogeneity of the included studies. Studies will also be assessed for how well and clearly they described the diagnostic methods and definitions used to identify infertility etiology. The rigor by which diagnostic tests are applied to the causative determination of infertility will also be sought from relevant reports.
Adapted from the Maternal Morbidity and Mortality Study, a scoring system is proposed to assess the adequacy of basic study and reporting characteristics (see Table 2). This scoring system will be used to assign some evaluation of quality to each study.
Studies will be categorised as:

- Excellent quality if all six criteria are adequate
- High quality if four or five criteria are adequate
- Medium quality if two or three criteria are adequate
- Low quality if none or only one criterion is adequate

Table 2. Quality assessment criteria for studies

	Adequate	Inadequate
Sampling	Random, consecutive, etc.	Selected groups, etc.
Power calculation	Study calculates and meets power requirements; or explains why this was not possible	No discussion or study underpowered with no explanation

Description of population	Type and characteristics of population and type of setting are specified	Either of them not specified
Follow-up / completeness of data	Reported and <20% loss	Not reported or >20% loss
Definition of outcome / description of diagnostic procedure	Etiology – definition and diagnostics reported Infertility – definition reported, special efforts	Etiology – definition or diagnostics not reported Infertility– no definition or no special efforts

4.7 Analysis plan

The strategy to identify appropriate methods for analysis of the data will be developed in consultation with statisticians and other experts in epidemiology. It is expected that several possibilities for data analysis will include techniques for pooling results and methods to use the results in various proposed models.

It is also hoped to be able to explore the possible relationship between identified patterns of certain types of infertility with the prevalence of particular categories of morbidity or mortality identified in the Maternal Morbidity and Mortality study. If this is deemed possible, attributable cause calculations may well be very useful for trying to determine if certain categories of infertility carry with them a greater risk of subsequent morbidity or mortality if the patient conceives and carries a pregnancy.

5. Search strategy for identification of studies

The search strategy employed will be a modified version of the strategy applied and detailed in the WHO systematic review of maternal morbidity and mortality. This review will have no language restrictions. Reviewers will be from geographical diverse areas and will review articles from languages in their area. Reports in other languages will be translated into English. The review will cover published and unpublished studies and data dated from 1999 to 2004.

5.1 Electronic databases searching

As in the WHO maternity and mortality systematic review the electronic databases that will be searched from 1999 on are: Medline, Popline, Cochrane Library, CAB, Sociofile,

CINAHL, Econlit, EMBASE, BIOSIS, PAIS International, and the Latin American and Caribbean Health Science Information (LILACS). Search strategies will be customised for each electronic database according to their individual subject headings and searching structure.

As well as these electronic databases, regional WHO on-line databases will be searched. These databases include: African Index Medicus (AIM), Index Medicus for the Eastern Mediterranean Region (IMEMR), and Index Medicus for the South-East Asian Region (IMSEAR). These searches will be run by the reviewers at WHO/HQ in Geneva except for that of IMSEAR that will be run at the WHO regional office of the South-East Asian Region by the person responsible of the database. Again a specific strategy will be designed for each database in consultation with the research librarian staff.

5.2 Other electronic searching

Existing web pages from Ministries of Health in all countries will be searched for official information and its source. An internet search using “Google” searching engine with the terms “infertility prevalence” and "causes of infertility" will be performed. This is expected to result in a significant number of entries, many dealing with the provision of Assistive Reproductive Technologies (ART). As such, an advanced “Google” or other database search engine that will enable Boolean logic search strategies will be employed and a search strategy designed in conjunction with a research librarian.

5.3 Infertility treatment registries/services

There are several known databases for ART and other treatments of infertility. There is significant variation as to the data collected and with respect to who must submit information. Regional reviewers will have the responsibility of identifying and contacting clinics providing these services to determine if they submit data to a registry or if they maintain their own statistics/database. External or internal validation of their data will be ascertained. Information gathered will be specific to the research question of the prevalence of infertility and its etiologic causes not the outcome of ART treatment. A specific data extraction form will be designed for collecting this data.

Regional reviewers will also identify the relevant international, national and organizational databases (Human Fertilization and Embryology Authority [UK],

European Society for Human Reproduction and Embryology [EU], American Society for Reproductive Medicine [USA]). Central reviewers will contact these sources directly or through assigned regional reviewers.

5.4 Hand searching

Manual searching of relevant data sources will be conducted. These will include the WHO Reproductive Health databases kept in the Department of Reproductive Health and Research at WHO will be searched for relevant references. As well, all documents identified will be screened for relevant data, projects or contacts. Reference lists and bibliographies from review articles will be scrutinized, as will proceedings and abstract books of congresses. Relevant references and authors will be contacted whenever appropriate.

5.5 Personal contacts

Regional reviewers will be asked to communicate with relevant identified experts in their assigned areas. Reviewers to identify additional relevant resources will contact regional WHO contacts. Advocacy groups or other agencies may also be contacted. All non-traditional contacts will be documented and noted in a central on-line database.

5.6 Communication strategies

A summary of the proposed research for publication in several journals, will be prepared. The geographically distributed reviewers will be asked to contact relevant journal editors for possible inclusion of the objectives of the review in editorial sections. It is hoped that this will reach a broad audience, resulting in the identification of relevant data, particularly that in non-English areas, that would be otherwise unknown to the reviewers. Data obtained in this manner will be identified in order to ascertain how effective this is as an additional search strategy.

6. Description of studies

As in the Maternal Morbidity and Mortality study, the characteristics of the studies evaluated will be displayed in a table outlining the study methods, participants and measured outcomes. The table will list the studies by the year of data collection and by

country. For countries with multiple reports, first author or agency name will list the studies alphabetically.

7. References

1. Rutstein, S. and Shah, I. 2004. Infecundicity, Infertility, and Childlessness in Developing Countries. DHS Comparative Reports No. 9 Calverton, Maryland, USA:ORC Macro and the World Health Organization.

2. Farley T. 1986. The epidemiology of infertility in Europe and in Africa. Paper presented at the International Congress on Current status of Infertility and Conception Control in Europe and in Africa. Gubbio, Italy, 20 –21 June, 1986. In Lauritsen, J. et al.1986. Artificial Reproduction: Report on a Consultation and Research Findings. Copenhagen. 28 –29 March 1985. [Full Text]

3. Infertility. A tabulation of available data on primary and secondary infertility. Programme on Maternal and Child Health and Family Planning. Division of Family Health. World Health Organization, Geneva. 1991.[Full text]

4. Butler,P. What constitutes sexual health? Progress in Reproductive Health Research. 2004 67:3-4.

5. Macklin RB. Reproductive technologies in developing countries. Bioethics.1995 Jul;9(3-4):276-82. [Abstract]

6. Zaba B, Campbell OM. The impact of eliminating sterility on population growth. Sex Transm Dis. 1994 Sep-Oct;21(5):289-91. [Abstract]

7. Vayena, E. Rowe, P. and Griffin, P. eds 2002. Current practices and controversies in assisted reproduction: Report of a WHO meeting. Geneva: World Health Organization. xv-xvi. [Full text]

8. Lunenfeld B, Van Steirteghem A; Bertarelli Foundation. Infertility in the third millennium: implications for the individual, family and society: condensed meeting report from the Bertarelli Foundation's second global conference. Hum Reprod Update. 2004 Jul-Aug;10(4):317-26. Epub 2004 Jun 10. [Abstract].

9. Walraven G, Scherf C, West B, Ekpo G, Paine K, Coleman R, Bailey R, Morison L. The burden of reproductive-organ disease in rural women in The Gambia, West Africa. Lancet. 2001 Apr 14;357(9263):1161-7.[Abstract]

10. Araoye MO. Epidemiology of infertility: social problems of the infertile couples. West Afr J Med. 2003 Jun;22(2):190-6. [Abstract]

11. Boerma, JT and Urassa, M. Associations between female infertility, HIV and sexual behaviour in rural Tanzania. In Boerma, JT and Urassa, M. (eds.) Women

and infertility in sub-Saharan Africa: A multi-disciplinary perspective. 2001. Royal Tropical Institute, Amsterdam: 179 –185.

12. Basso O, Olsen J. Subfecundity and neonatal mortality: longitudinal study within the Danish national birth cohort. BMJ. 2005 Feb 19;330(7488):393-4. Epub 2005 Feb 4. [Abstract] [Full Text]

13. Joffe M, Li Z. Association of time to pregnancy and the outcome of pregnancy. Fertil Steril. 1994 Jul;62(1):71-5. [Abstract]

14. Basso O, Weinberg CR, Baird DD, Wilcox AJ, Olsen J; Danish National Birth Cohort. Subfecundity as a correlate of preeclampsia: a study within the Danish National Birth Cohort. Am J Epidemiol. 2003 Feb 1;157(3):195-202. [Abstract]

15. Talbott EO, Zborowski JV, Rager JR, Boudreaux MY, Edmundowicz DA, Guzick DS. Evidence for an association between metabolic cardiovascular syndrome and coronary and aortic calcification among women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2004 Nov;89(11):5454-61. [Abstract]

16. Loverro G. Polycystic ovary syndrome and cardiovascular disease. Minerva Endocrinol. 2004 Sep;29(3):129-38. [Abstract] [Full Text]

17. World Health Organization. Systematic Review on the epidemiological evidence for maternal morbidity and mortality 1997-2002. Study protocol. Draft. UNDP/ UNFPA/ WHO/World Bank Special Programme of Research, Development, and Research Training in Human Reproduction Department of Reproductive Health and Research, World Health Organization, Geneva

18. World Health Organization 1990. Research in Human Reproduction. Biennial Report 1988- 1989. Special Programme of Research, Development and Research Training in Human Reproduction. Geneva World Health Organization. International Classification of Disease (ICD-10). WHO | International Classification of Diseases (ICD)