EU Public Health Program 2007106

AMIEHS

Avoidable mortality in the European Union:
Towards better indicators for the effectiveness of health systems

Volume 1: Final report

August 2011

This report arises from the project AMIEHS which has received funding from the European Union, in the framework of the Public Health Program

Iris Plug, Rasmus Hoffmann and Johan Mackenbach (eds.)

Website: http://amiehs.lshtm.ac.uk/

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University of Debrecen
Hungary

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New Zealand

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Summary

Introduction

There is widespread consensus that there is a need for better indicators of the effectiveness of health systems. Health systems have three fundamental goals, improving health, providing services responsive to the needs of populations, and establishing systems of fair financing. This study has focused on the first of these.

One of the earliest ways of assessing the contribution of health care to population health outcomes is based on the concept that deaths from certain causes should not occur in the presence of timely and effective health care. This concept has been operationalised and given a variety of terms including 'avoidable/amenable mortality' and 'mortality either amenable or avoidable to medical/health care'. This approach attracted considerable interest in the 1980s, gaining momentum through the European Commission's Concerted Action Project on Health Services and 'Avoidable Deaths', launched in the early 1980s, and culminating in publication of the European Community Atlas of 'Avoidable Death' in 1988, a major contribution that has since been updated twice.

There are several reasons why there is an urgent need for renewed research efforts in this area. The first is that the older work needs to be updated. The majority of work on amenable mortality, including the 3rd and last edition of the EC Atlas of 'Avoidable Death' published in 1997, use a very limited group of causes of death which, given the remarkable changes in health care in subsequent years, seems no longer justifiable as it is likely to underestimate the 'true' impact of health care on population health. The second reason is that this selection of causes of death was based on an informal procedure, drawing heavily on expert opinion, and the validity of these causes of death as indicators of the effectiveness of health care effectiveness has never been adequately demonstrated. Since the first publications on the concept of 'amenable mortality', scientific standards for the measurement and analysis of population health have improved, making it necessary to apply these rigorous standards to the selection of indicator conditions. Finally, much of the work on 'amenable' mortality limited this concept to deaths before, for example, the age of 65, a figure that seems inappropriately low in the light of life expectancies that are now about 75 years for men and 80 years for women in many countries.

Aim and objectives

Although there have been a variety of terms to describe conditions from which death should not occur in the presence of timely and effective care, the AMIEHS project uses the term "amenable mortality".

The general aim of the AMIEHS project was to develop an agreed definition of amenable mortality for Europe, and to derive a set of indicators of the effectiveness of health systems that can be used in routine surveillance systems.

The specific objectives were:

1. To identify causes of death that can now be considered ‘amenable’, based on systematic reviews of the literature.
2. For five countries, to analyze the introduction of health care interventions that might have reduced amenable mortality.
3. To build a harmonized database of trends in amenable mortality in 1971-2005 in seven European countries.
4. To evaluate the effect of coding changes and to develop correction factors to adjust observed mortality trends.
5. To determine whether the introduction of innovations coincided with declines in mortality from selected amenable causes.
6. To develop and agree on a set of validated amenable mortality-based indicators, through expert consensus.
7. To illustrate the use of amenable mortality indicators by preparing an e-atlas of variations in amenable mortality.

Results

For this project, we defined ‘amenable mortality’ as causes of death for which mortality rates are likely to reflect variations in the effectiveness of health care, with health care being limited to primary care, hospital care, personalized public health services (e.g. immunisation and screening).

In a first step, we pre-selected causes of death for which a considerable decline in mortality has occurred since 1970, and for which there was still a sufficient number of deaths in 2000 to allow a meaningful analysis of between-country variations in mortality. Using data on mortality from 644 specific causes of death in one large European country, England and Wales, we identified 54 conditions for which mortality declined more than 30% between 1979 and 2000, and for which the number of deaths in 2000 exceeded 100. England and Wales was selected firstly because it was among the largest European countries with consistent data over this period (Germany was complicated by reunification) and also it was one where any changes in coding were already well understood. We considered that any number smaller than this would vary too much by chance when applied to smaller countries.

For these conditions we conducted a systematic review of the literature in order to identify health care interventions which were introduced after 1970 and which, according to evidence from patient or population-level studies, have effectively reduced mortality from these conditions. Out of the original list of 54 conditions, 14 conditions fulfilled this criterion. The strength of the evidence, however, was variable, with only few interventions having the highest grade (evidence from systematic review or meta-analysis) and many interventions being underpinned by evidence from single trials or observational studies only. The review also highlighted the common (and entirely legitimate) approach of using existing treatment as the control in

randomised controlled trials, which however means that it is difficult to ascertain the actual effectiveness (as opposed to doing nothing) of most interventions. It also showed that there are remarkably few studies of the population-level effects of introducing new interventions.

For these candidate interventions we sought to identify the timing of introduction in seven European countries. This was done by sending questionnaires to partners in these countries, and by conducting reviews of the international and national literature. This also provided the approximate period of introduction in each of the countries, and, using information on the delay between introduction and a possible mortality-lowering effect, the approximate period in which a decline in mortality could be expected. Again, this task was difficult as there was often a period over which interventions were introduced, with no obvious beginning and end point. These estimates were obtained for 14 conditions, and showed considerable between-country variation in the timing of introduction of the interventions.

For each of these conditions we obtained mortality data for the seven countries (Estonia, France, Germany-east, Germany-west, The Netherlands, Spain, Sweden, UK) covering the period 1970-2005.

Possible coding changes that might influence mortality trends were identified by an automated jump detection method which was applied to time series data by cause from each country. If jumps were detected that had not been previously documented, their plausibility was checked with national data producers. We found a considerable number of coding changes which needed correction. Correction factors were derived and these were applied to create a consolidated database.

For each of the 14 conditions, mortality trends were analyzed using regression analyses. We applied Joinpoint regression to identify points in time ('knots') at which the mortality trend changed significantly (e.g. a mortality decline started or accelerated). Although there was often a general mortality decline for most of these conditions, this was not uniform and there were striking variations between countries in the mortality trends as well as in the timing of 'knots'. We related these 'knots' to the approximate periods in which a decline in mortality from the introduction of interventions could be expected, and found slightly more 'matches' between the two than could be expected to occur by chance alone. Matches were found in a majority of countries for a few conditions only (i.e., cerebrovascular disease, ischemic heart disease, HIV/AIDS, and colorectal cancer). However, even in these cases mortality trends were only partly associated with the periods identified as capturing the introduction of health care interventions. Applying an age-limit (<75 years instead of all ages) added hypertension, rheumatic heart disease and leukaemia to the list, but excluded colorectal cancer and ischaemic heart disease.

The results of each of the preceding steps were summarized and 23 experts involved in the use of health care indicators were asked to assess the likelihood that variations in mortality from the 14 selected conditions reflect variations in the effectiveness of health care. In a Delphi procedure with two rounds, the experts reached consensus on only 3 out of these 14 conditions (colorectal cancer, cervical cancer, and cerebrovascular disease).

An electronic atlas was prepared which presents mortality from 45 potentially amenable conditions for 30 European countries.

1. Introduction

1.1 Background

Health systems have three goals: to improve the health of the populations they serve, to respond to the reasonable expectations of those populations, and to collect the funds to do so in a way that is fair[1]. The first of these, health improvement, has traditionally been captured using broad measures of mortality, such as total mortality, life expectancy, premature mortality or years of life lost, while more recently this has been supplemented by measures of the time lived in poor health, exemplified by the use of disability adjusted life years.

These measures are being employed, increasingly, in comparisons among and within countries, as a means of assessing the performance of health systems. Their main advantage is that the data are generally available. They do, however, have some important drawbacks, the most important of which is that they fail to distinguish that component of the overall burden of disease that is attributable to health systems and that which is attributable to actions initiated in sectors other than the health sector. The 2000 World Health Report sought to overcome this problem by adopting a very broad definition of a health system as "all the activities whose primary purpose is to promote, restore or maintain health".[1] Thus, by means of a somewhat circular logic, it was possible to justify the use of disability adjusted life years lived as a measure of performance. However, in many cases, policy-makers will wish to examine a rather more narrow question, how is a particular health system performing in the delivery of health care?

One approach makes use of the readily available mortality data at population level in many countries, and is based on the concept that deaths from certain causes, and at certain ages, should not occur in the presence of timely and effective health care. This concept originates from the Working Group on Preventable and Manageable Diseases led by David Rutstein of Harvard Medical School in the USA in the 1970s.[2] The group introduced the notion of 'unnecessary untimely deaths' that should be considered as 'sentinel health events' and so providing a marker of the quality of care.

Charlton et al. (1983) were the first to apply this concept at the population level to analyse regional variation in mortality in England and Wales in 1974-78, also introducing the terms 'avoidable deaths' and '[conditions] amenable to medical intervention'.[3] Based on Rutstein's list they selected 14 disease groups chosen to reflect different aspects of health care, including primary care, general practice referrals to hospitals and hospital care, with age limits set for each cause, most often 5-64 years.[4] The concept was subsequently adopted widely, particularly in Europe, applying it to routinely collected mortality data. It gained momentum with the European Commission Concerted Action Project on Health Services and 'Avoidable Deaths', established in the early 1980s. Building on the work by Charlton et al. (1983)[4], the project led to the publication of the European Community Atlas of 'Avoidable Death' in 1988[4], a major work that has been updated twice.[6 7] Subsequent work has expanded the list of causes of death considered avoidable, reflecting advances in health care, and increased the upper age limit for these deaths, reflecting improvements in life expectancy.[8]

Much of the work on avoidable mortality dates back to the 1980s and early 1990s. More recent work by Nolte and McKee (2004), which reviewed the available evidence on avoidable mortality, demonstrated that the concept may serve as a potentially useful tool to assess the quality and performance of health systems.[8] That review applied an amended version of the original lists of avoidable causes of death to countries in the European Union (EU-15), providing clear evidence that improvements in health care have had a measurable impact on population health in the region during the 1980s and 1990s. However, their review also highlighted several limitations of the concept of avoidable mortality and corresponding indicators as they have been used so far, suggesting that there is much that can be achieved by revisiting and updating the list of avoidable causes of death to reflect the changing scope of health care.

1.2 Rationale for the AMIEHS project

The need for renewed research efforts in the area of avoidable mortality can be seen on several levels: First, there is a need to update the older work, both with regard to the selection of causes of death and the countries included in the analysis. With the possible exception of work by Tobias and Jackson[9], analyzing avoidable mortality in New Zealand, the majority of work on avoidable mortality, including the third and last edition of the EC Atlas of 'Avoidable Death' of 1997[7], uses a very limited group of causes of death. Given the almost unprecedented changes in health care since the concept was first applied in the early 1980s, previous selections of causes of death seem no longer justifiable as they likely underestimate the 'true' contribution of health care to population health. Second, much of the work on 'avoidable' mortality limited this concept to deaths before, for example, the age of 65.[8] This figure seems inappropriately low in the light of life expectancies that are now being achieved in many European countries. More recent work has used an upper age-limit of 75 years but that work did not take account of the large difference in life expectancy between men and women (about 75 and 80 years respectively). This issue has so far received little attention and needs to be addressed in a systematic way. Finally, the 1997 edition of the European Community Atlas of 'Avoidable Death' presents data for 1985-1989 only and covers those countries that were then members of the EU (excluding Luxembourg).[7] A separate 'Atlas of leading and 'avoidable' causes of death', also published in 1997, presented corresponding data for 14 countries in Central and Eastern Europe, but again covering the late 1980s only.[10] As the European Union has subsequently expanded with an additional 12 countries, there is an urgent need to update this work.

1.2.1 Terminology

The main aim of the AMIEHS project is to create a list of conditions for which variations in mortality between countries are likely to reflect variations in performance of health care systems in 2000-2005. In other words conditions that are amenable to medical interventions. In order to avoid confusion in the AMIEHS study the term "amenable mortality" instead of "avoidable mortality" will be used.

1.3 The AMIEHS project

The AMIEHS project (Amenable Mortality in the European Union, towards better Indicators for the Effectiveness of Health Systems) began in March 2008. The overall objective of the AMIEHS project, funded under the European Union's Public Health Programme and implemented through the Executive Agency for Health and Consumers (EAHC) (Agreement no. 2007106), is to develop an agreed definition of amenable mortality for Europe, and to derive a set of validated amenable mortality-based indicators of the effectiveness of health systems which can be used in routine surveillance systems.

The AMIEHS project brings together partners in seven EU countries. It is led by the Department of Public Health at Erasmus Universitair Medisch Centrum (Erasmus MC), Rotterdam, The Netherlands, and coordinated jointly with the London School of Hygiene & Tropical Medicine, London, United Kingdom. Further partners are: Uppsala University, Sweden; Institut National de la santé et de la recherche médicale (Inserm), France; University of Tartu, Estonia; NRW Institute of Health and Work (Liga), Germany; and University of Valencia, Spain. The project has established an Advisory board comprising international experts and stakeholders to ensure a high level of scientific quality and policy relevance.

The project was scheduled for a period of 36 months with a total of ten work packages to be completed, of which 7 work packages involve the identification of indicators (WP 1-7) and 3 work packages involve coordination (WP 8), dissemination (WP 9) and evaluation (WP10) of the project. In this final report we describe the complete work of the AMIEHS project, which covers the period between 1-3-2008 and 1-7-2011. This report summarizes the main results of the AMIEHS project and presents the results from the individual work. For the seven participating countries a country specific report was prepared in which trends and associations are interpreted by the individual partners, these are included in appendix G. For this study a website was constructed: http://amiehs.lshtm.ac.uk/

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2. Identification of amenable causes of death (Results of work package 1)

Authors: Bernadette Khoshaba, Martin McKee
Affiliation: London School of Hygiene and Tropical Medicine, United Kingdom

2.1 Introduction

since 1970; a The concept of amenable mortality was developed by Rutstein and colleagues in 1976[1]. It was based on the premise that deaths from certain causes, and at certain ages, should not occur in the presence of timely and effective care. Subsequent work has expanded the list of causes of death considered amenable, reflecting advances in health care, and increased the upper age limit for these deaths, reflecting improvements in life expectancy[2]. The concept has also been refined to include differentiation of causes amenable to the health care system and those to public health policy[3], while specific causes have been partitioned into the proportion to which reductions are attributable to primary, secondary, and tertiary actions[4].

In recent years, amenable mortality has undergone something of a renaissance. In part this reflects the much greater interest in performance of health systems, stimulated by the 2000 World Health Report, with improved tools being sought avidly by policy-makers seeking to determine whether they were getting value for money. An example was a study showing that deaths from amenable mortality in the USA around the year 2000 had hardly changed at a time when other industrialised countries were experiencing substantial declines.[5] As a consequence, a number of governments and international agencies explored how rates of amenable mortality could be used for regular monitoring and comparison of health systems. However, this represented a departure from how amenable mortality had been used, with the original aim being to identify deaths that would point to specific aspects of care requiring more detailed examination. For this reason, it was timely to reflect on whether the concept of amenable mortality could indeed be adapted when used in the aggregate to assess the performance of health systems.

2.1.1 Objectives

This report describes the outcome of work package 1 of the AMIEHS Project, which sought to develop a set of indicators of health system performance based on the concept of amenable mortality. In this limited task we identified causes where death rates were falling and where evidence was available that deaths could be avoided due to a discrete intervention introduced year chosen because of the ease of availability of mortality data. This pre selection of causes of death enabled the next stage of the project to be undertaken, whereby trends in deaths from such causes in a range of countries were correlated with the introduction of the interventions in question. Consequently, our findings should not in any way be seen as generating a comprehensive list of deaths amenable to health care. Specifically, we excluded causes where there was evidence that despite effective interventions these were introduced at a time of rising incidence, so that the net effect was that mortality was increasing. There were also causes where deaths were falling but, as far as we could tell, this was due to the combined increment, and on the available evidence inseparable, effect of innovation, improved coverage, and quality of a range of interventions and innovations. An example would be where an effective drug was developed and used initially on a small group of patients, with subsequent

lowering of the threshold for treatment, leading to expansion of the population treated, increased expertise in managing side effects, and subsequent safer preparations were developed, or where an improved surgical technique was introduced but at the same time as other improvements in anaesthetic technique. Finally, there were causes where the continued benefits of treatment were apparent, but where the key intervention was introduced before, and in some cases long before, 1970. Examples include many common infections treated by antibiotics, or diabetes treated by insulin. These were all causes amenable to health care but not relevant to the next stage of the AMIEHS project, in which evidence was collected on the timing on intervention introduction which corresponded to the conditions identified here in several European countries.

2.1.2 Defining the desired properties of amenable mortality indicators

Evidence of decline in mortality

For a cause of death to have been selected for the next stage of the AMIEHS project, it had to demonstrate that death rates had fallen by an appreciable amount. Only then was it possible to ascertain whether this was due to improvements in health care. It is recognised that there are conditions where health care has been able to reduce mortality yet overall death rates have increased, as incidence has outpaced health care progress. An example is malignant melanoma where there have been modest improvements in survival due mainly to earlier detection but where, at least in Northern European populations; there has been a marked increase in incidence due to greater exposure to ultra violet light.

Hence, an initial screen of potential causes of death should identify those where deaths have fallen appreciably. Given the scope for artefact to arise as a result of coding of cause of death, we selected one country (England and Wales) and the interval between the beginning and end of the use of the 9th Revisions of the International Classification of Diseases (ICD) (1979-2000). This provided a 21 year period during which it would be anticipated that any benefits attributable to health care would be seen.

Sufficient numbers

An indicator of amenable mortality (AM) is of little use if it causes no or only a few deaths each year. Hence, it was felt necessary to impose a threshold for inclusion, where causes of less than a given number of deaths in one of the larger European countries would be excluded. While this threshold is, inevitably, somewhat arbitrary, for the present purposes we selected 100 deaths in England and Wales in 2000.

Specificity

Some registered causes of death were underlying conditions, with affected individuals dying from a wide range of other disorders, such as infections. Others were complications of underlying disorders, such as septicaemia. It was difficult to ascertain what specific interventions accounted for any observed decline and therefore we excluded these conditions from consideration. Similarly, there were some causes of death where it was not possible to identify a plausible intervention.

Timing of effect

In its original conceptualisation, amenable mortality included some conditions where medical care could do little to prevent death once the disease process had occurred but where the onset of the disease could be prevented by health promotion activities. This is exemplified by lung cancer, where, it was argued, health

professionals could be effective in preventing people smoking or encouraging them to quit. However, assuming they were successful, the deaths that would then be avoided would occur several decades later. Clearly, this is incompatible with the idea that contemporary rates of amenable mortality reflect the current performance of health systems. Hence, only those deaths that could be prevented by contemporary interventions were included. The definition of contemporary is inevitably somewhat arbitrary but we set it at five years, this a time period used to assess what is popularly considered as “cure” in analyses of cancer survival.

Direct evidence of improved survival (lead time bias)

Cancers are unusual because it is possible to use data from registries to identify improvements in survival. Although data need to be interpreted with some caution because of known problems, such as lead time bias, the absence of an improvement in 5-year survival indicates that a condition would not be included in a list of potential indicators. We extracted changes in cancer survival from successive waves of the EUROCARE study.

Evidence of impact of health care on observed decline in mortality

Where possible, we obtained previous research that had examined reductions in mortality at a population level and the contribution of health care made to those reductions. It was often necessary to draw on natural experiments, where it was possible to determine when new treatments were introduced. An example is the introduction of HAART for patients with AIDS, where death rates fell very rapidly. In other cases, even where detailed data were unavailable, it was possible to infer the impact of health care where there had been wider system change. An example is the political transition in Eastern Europe around 1990. The opening of borders to modern pharmaceuticals and ideas of evidence-based medicine made it possible to provide treatment that was previously denied to sufferers from many chronic diseases. Thus, in countries such as Estonia, there was a rapid decline in mortality from stroke, almost certainly as a result of better treatment of hypertension, at a time when such deaths were increasing in neighbouring Russia.

Evidence of effectiveness of interventions

Where possible, evidence of mortality reduction was sought from clinical trials. However this often proved to be difficult. Firstly, many trials measured intermediate outcomes, rather than mortality itself. Second, most compared incremental advances in treatment with what went before, rather than with no treatment. Third, randomised controlled trials also face the problem of external validity, as they often exclude both children and older people, those with co-morbidities, and historically, women. Further evidence of effectiveness was sought from other types of studies i.e. observational, natural and historical data. In addition, a ‘grading’ was applied to the level of evidence available during the search period of this study.

Grading of evidence

The numerical rating below was used to grade the evidence:

Evidence of decline attributable to health care

3 – Evidence from population-based registers (e.g. cancer registries) of reduction in mortality among known cases

2 – Published studies describing decline in mortality at population level where investigation has identified health care interventions as the most likely explanation

1 – Published studies describing decline in mortality at population level where investigation has identified health care interventions as one among several explanations

Evidence of effectiveness of interventions

4 – Evidence from systematic reviews or meta-analysis

3 – Evidence from one or more randomised controlled trial

2 – Evidence from observational studies

1 – Consensus statements or expert opinions

Timing of interventions

For these purposes, we sought conditions where we assessed the impact of effective treatment since 1970, key interventions that were widely available long before this period were excluded. However, as noted above, conditions that were excluded for this exercise were retained in a separate comprehensive list of conditions amenable to health care.

System boundaries

One of the most difficult definitional issues in assessing health system performance is how to define the borders of a health system. The 2000 World Health Report adopted an essentially pragmatic definition as it was necessary to include all of the WHO's 193 member states, the majority of which had no functioning system of vital registration and certainly no possibility of ascertaining causes of death. As a consequence, it defined the health system extremely broadly as all the activities whose primary purpose is to promote, restore or maintain health. This included a range of inter sectoral actions. It is, however, difficult to justify holding the health system to account for actions that others must take. For this reason, we proposed that the boundaries were to be drawn more tightly, to include interventions delivered by those working what is unambiguously the health care system but also those developed by public health agencies, such as immunisations and screening for cancer.

2.2 Developing a list of core AM indicators

'Operalisation' of the desired properties of indicators

In order to produce a core list of AM conditions, each of the above criteria were operationalised and applied in a stepwise approach using the mortality data set of the Office of National Statistics for England and Wales and the interval between the beginning and end of the use of the 9th Revisions of the International Classification of Diseases (ICD) between 1979-2000. Of 644 3 digit ICD codes, 544 had one or more deaths in 2000 (Step 1). 160 codes had 100 or more deaths in 2000 (Step 2) and, of those, 54 exhibited a decline in age-standardised mortality of 30% or more (Step 3). These steps are set out in Figure 2.1.

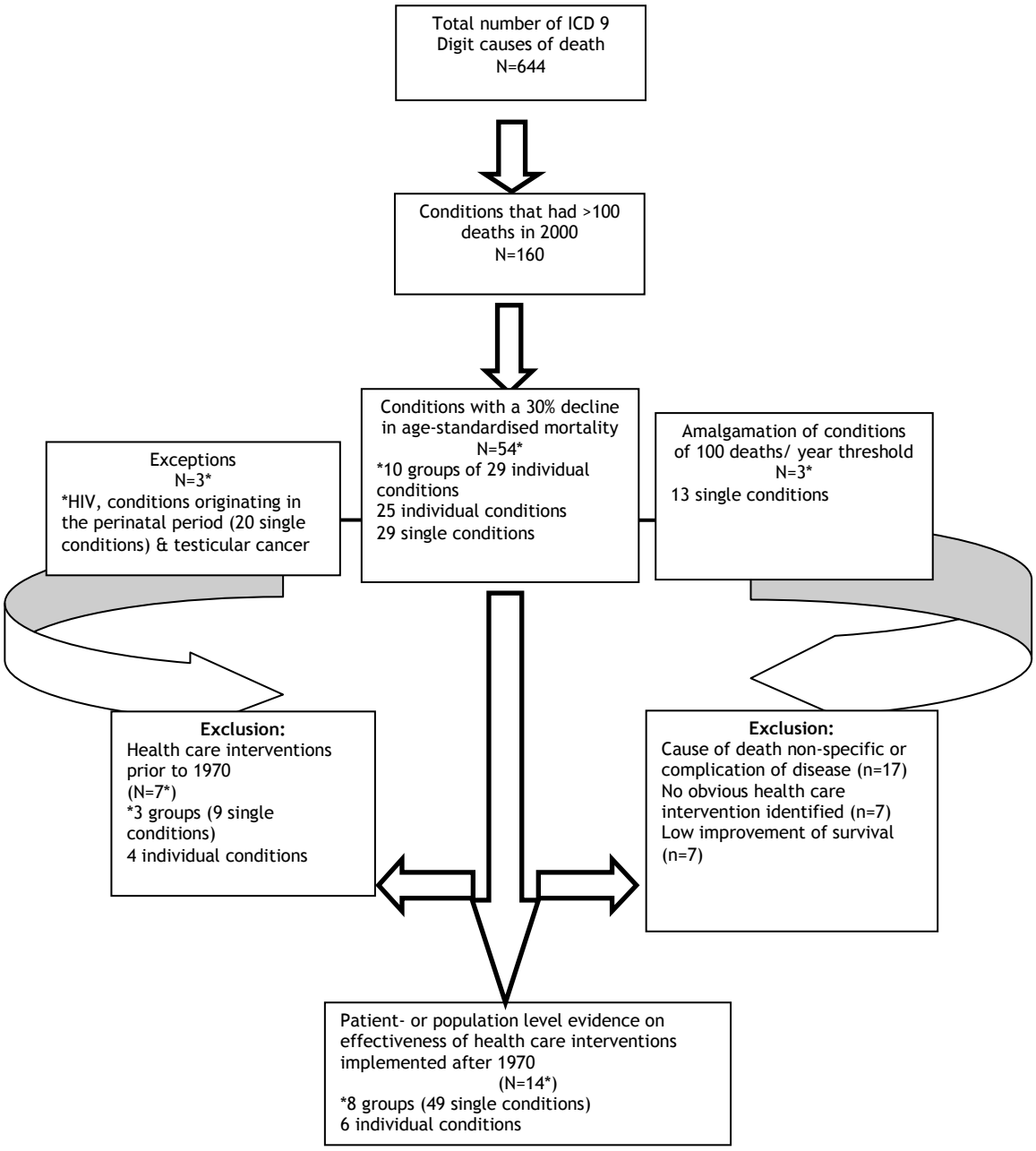

Figure 2.1 Flowchart illustrating the operationalisation of the desired properties of AM indicators

We then inspected the results (Table 1, appendix A) to identify ICD codes where, although individually falling below the threshold of 100 deaths/ year, they could logically be amalgamated to form groups that exceeded the threshold (Step 4). We have also grouped those causes that are individually above the threshold but form a clinically coherent grouping linked to a single intervention (Table 2.2). However, we recognised that further work would be necessary to consider causes of death that, while maybe few in England and Wales, are more common elsewhere.

Table 2.1 Conditions where, although the number of deaths in 2000 in a specific 3 digit ICD code was under 100, a combination of codes formed a clinically coherent grouping.

ICD-9	Condition	ASDR 1979	ASDR 2000	Percentage decline in ASDR	N deaths 1979	N Deaths 2000
550-553	Abdominal hernias	0.638967	0.307849	52%	362	176
320, 322	Meningitis	0.535313	0.318414	41%	243	161
880-886	Falls (excluding fall cause unspecified and Other and unspecified fall)	1.707071	1.14104	33%	879	617

We then screened the causes remaining after Step 4 and excluded those, such as septicaemia, where the cause of death was most often one of the terminal events in a complex combination of disorders, and where successful treatment would require a range of interventions (e.g. resuscitation, antibiotics, treatment of organ failure, and treatment of the underlying condition). We also excluded those causes of death where the timing of the terminal event precluded intervention (e.g. sudden unexplained death). A summary of potentially included causes and aggregation into clinically meaningful groups are depicted in 2.2.

Table 2.2 Summary of potentially included causes – aggregation into clinically meaningful groups and justification for further investigation or otherwise

ICD 9 code	Cause of death	Notes	Inclusion/ Exclusion YES/NO	Reason for Exclusion/ exceptions
-	*HIV	Potentially amenable	YES	HIV not coded in the 9th revision of the ICD
11	Pulmonary tuberculosis	Potentially amenable	NO	Intervention prior to 1970
151	Malignant neoplasm of stomach	Potentially amenable	NO	No obvious healthcare intervention
154	Malignant neoplasm of rectum, recto sigmoid junction and anus	Potentially amenable	YES	
156	Malignant neoplasm of gallbladder and extra hepatic bile ducts	Improvement in survival but only to 16% at 5 years from cancer registry data	NO	Low improvement in survival
162	Malignant neoplasm of trachea, bronchus and lung	No improvement in survival	NO	Low improvement in survival
170	Malignant neoplasm of bone and articular cartilage	Potentially amenable	NO	No obvious healthcare intervention
173	Other malignant neoplasm of skin	Non-specific	NO	Non-specific
180	Malignant neoplasm of cervix uteri	Potentially amenable (no improvement in survival but contribution of screening)	YES	
182	Malignant neoplasm of body of uterus	No improvement in survival from cancer registry data	NO	Low improvement in survival
184	Malignant neoplasm of other and unspecified female genital organs	Non-specific	NO	Non-specific
186	*Malignant neoplasm of testes	Potentially amenable	YES	Mortality rates remain high in other European Union countries
193	Malignant neoplasm of thyroid gland	Potentially amenable	NO	No obvious healthcare intervention
201	Hodgkin's disease	Potentially amenable	YES	
320	Bacterial Meningitis	Potentially amenable (Grouped as meningitis)	NO	Intervention prior to 1970
322	Meningitis of unspecified cause			
332	Parkinson's disease	Death likely to be due to various non-specific complications and co-morbidities	NO	Cause of death non-specific or complication of disease
394	Diseases of mitral valve	Potentially amenable (Group as rheumatic heart disease)	YES	
396	Diseases of mitral and aortic valves			
402	Hypertensive heart disease	Potentially amenable (Group as hypertension)	YES	
403	Hypertensive renal disease			
410	Acute myocardial infarction	Potentially amenable (Group as ischaemic heart disease)	YES	
416	Chronic pulmonary heart disease			
424	Other diseases of endocardium			
428	Heart failure	Potentially amenable	YES	
429	Ill-defined descriptions and complications of heart disease	Non specific	NO	Cause of death non-specific or complication of disease
430	Subarachnoid haemorrhage	Potentially amenable – consider inclusion within hypertension	YES	
431	Intracerebral haemorrhage	Potentially amenable (Group as cerebrovascular disease)	YES	
434	Occlusion of cerebral arteries			
436	Acute but ill-defined cerebrovascular disease			
437	Other and ill-defined cerebrovascular disease			
440	Atherosclerosis	Potentially amenable	NO	Low improvement in survival
466	Acute bronchitis and bronchiolitis	Potentially amenable (Group as acute respiratory infection)	NO	Intervention prior to 1970
481	Pneumococcal pneumonia			
485	Bronchopneumonia, organism unspecified			

ICD 9 code	Cause of death	Notes	Inclusion/ Exclusion YES/NO	Reason for Exclusion/ exceptions
491	Chronic bronchitis	Potentially amenable (Group as COPD) (Evidence of coding shift from 491& 492 to 496 over period	NO	Intervention prior to 1970
492	Emphysema			
496	Chronic airways obstruction. not elsewhere classified			
493	Asthma	Potentially amenable	NO	Low improvement in survival
531	Gastric ulcer	Potentially amenable (Group as peptic ulcer)	YES	
532	Duodenal ulcer			
550	Inguinal hernia	Potentially amenable (Grouped as abdominal hernias)	NO	Intervention prior to 1970
551	Other hernia of abdominal cavity with gangrene			
552	Other hernia of abdominal cavity with obstruction, without mention of gangrene			
553	Other hernia of abdominal cavity without mention of obstruction, or gangrene			
574	Cholelithiasis	Potentially amenable	NO	Intervention prior to 1970
584	Acute renal failure	Potentially amenable (Group as renal failure)	YES	
585	Chronic renal failure			
590	Infections of kidney	Potentially amenable	NO	Intervention prior to 1970
710	Diffuse diseases of connective tissue	Non specific	NO	Cause of death non-specific or complication of disease
714	Rheumatoid arthritis and other inflammatory polyarthropathies	Death likely to be due to various non-specific complications and co-morbidities	NO	Cause of death non-specific or complication of disease
745	Bulbus cordis anomalies and anomalies of cardiac septal closure	Potentially amenable (Group as congenital heart disease)	YES	
746	Other congenital anomalies of heart			
747	Other congenital anomalies of circulatory system			
760-779	*Conditions originating in the perinatal period	Potentially amenable	YES	Coding issue in the UK of neonatal deaths in the year 2000
798	Sudden death, cause unknown	No obvious health care intervention	NO	No obvious health care intervention
812	Other motor vehicle traffic accident involving collision with another motor vehicle	Non-specific	NO	Non-specific
814	Motor vehicle traffic accident involving collision with pedestrian			
815	Other motor vehicle traffic accident involving collision on the highway			
880	Fall on or from stairs or steps	Non Specific Grouped as Falls (unspecified)	NO	Non-specific
881	Fall on or from ladders or scaffolding			
882	Fall from or out of building or other structure			
883	Fall into hole or other opening in surface			
884	Other fall from one level to another			
885	Fall on same level from slipping, tripping or stumbling			
886	Fall on same level from collision, pushing or shoving, by or with other person			
888	Other and unspecified fall			
910	Accidental drowning and submersion	No obvious health care intervention	NO	No obvious health care intervention
911	Inhalation and ingestion of food causing obstruction of respiratory tract	No obvious health care intervention	NO	No obvious health care intervention
950	Suicide and self-inflicted poisoning by solid or liquid substances	Potentially amenable (Group as suicide)	NO	Low improvement in survival
952	Suicide and self-inflicted poisoning by other gases and vapours			
984	Submersion (drowning), undetermined whether accidentally or purposely inflicted	No obvious health care intervention	NO	No obvious health care intervention

Literature searching in support of evidence decline in mortality

Having established a preliminary list of conditions for possible inclusion, we initiated the search for evidence. Once the putative "amenable" conditions had been established from the steps set out above, evidence was then sought to identify healthcare interventions that could in principle prevent deaths from such causes. A search of electronic bibliographic databases listed below was undertaken to identify such interventions, drawing on a range of sources of evidence, mainly involving high quality study designs such as randomised trials and systematic reviews of interventions but also including historical studies as well as trend analyses and observational studies. Information on interventions includes not only when they became available but, as important, when evidence that they were effective in reducing mortality was available. For example, drugs to treat hypertension were available from the early 1950s but were not widely used because of side effects. The rapid growth in their use followed both the development of safer products and the publication of research showing that treatment reduced deaths from stroke [6-10]. The literature search used the following electronic bibliographic databases: Medline, Embase, Scopus (abstract and citation database of research literature and quality web sources), CINAHL (nursing and allied health database), Web of Knowledge, Cochrane Library, Trip database and Zetoc (science journal and conference records). Reference lists from relevant articles and journals were followed up. The search terms (Box 2.1) were used in combination with each of the conditions shown in table 2.2. The search was not restricted to a particular time period (except of course that set by a given database, e.g. Medline covers articles that were published from 1950 onwards). Additional information was extracted from successive waves of the EUROCARE study, results of which are summarised in Appendix A, Table 2.

Box 2.1 Search terms AM indicators

Exp [CONDITION]
exp History /
exp Medical Care/
exp *mortality/
amenable mortality.mp.
avoidable mortality.mp.
exp Disease Surveillance/
exp Mortality/ or exp Trend Study/
exp Intervention Study/ or exp Early Intervention/
exp *Trends/
exp *therapeutic/
exp Outcome Measurement
exp Outcome Assessment
prevention.tw.
treatment.tw.
intervention.tw.
exp Sentinel Surveillance/ or exp Population Surveillance/
TREATMENT PLANNING/ or TREATMENT WITHDRAWAL/ or TREATMENT DURATION/ or DRUG TREATMENT FAILURE/ or TREATMENT RESPONSE/ or DRUG DEPENDENCE TREATMENT/ or TREATMENT CONTRAINDICATION/ or TREATMENT FAILURE/ or EMERGENCY TREATMENT/ or CONSERVATIVE TREATMENT/ or TREATMENT OUTCOME/ or TREATMENT INDICATION/
exp *population characteristics/ or exp *patient care management/ or exp *"delivery of health care"/ or exp *disease management/ or exp *medication therapy management/
exp *Prevention/ or exp *Hospital/ or exp *Public Health/

† Combinations of 'AND' or 'OR' were used on the above heading terms.

Exceptions

This process was undertaken to identify causes of death/ intervention combinations to be used in Work Package 2 and was designed to be as systematic as possible, working from observed reductions in mortality to evidence of effectiveness of interventions. However, it became apparent that this served to exclude one important condition, AIDS, because there was no code for it in the initial version of ICD-9. Consequently, it was treated as an exception and, as there was evidence of effectiveness of treatment, it was included. One other coding issue became apparent for neonatal deaths. The UK mortality data for all neonatal deaths in 2000 was coded as '0000'. Hence, due to this coding issue conditions originating in the perinatal period will also be treated under this exception rule and included. In addition, although the number of deaths from testicular cancer in 2000 was under 100, we are aware from other evidence that rates remain high in other European Union countries[11].

Pre-selection of amenable causes of death

This process generated a list of causes of death and evidence along with appropriate key interventions, presented in Table 2.3. This table catalogues interventions that, on the basis of the available evidence reviewed, may be considered as preventing deaths from the relevant causes they are listed against, and also interventions that in the majority of cases capture new advances in health care that have been developed or introduced after the initial intervention/s.

ICD Coding and quality scoring of available evidence

As the AM conditions had been identified through this process, the ICD coding for each of the conditions was amended and subsequently used in work package 4. Changes were based on the Eurostat pre-existing shortlist and Inserm-CépiDc coder's expertise. The nature and quality of the evidence for an effect of healthcare on mortality and for effectiveness of specific interventions is summarised in Table 2.4.

2.3 Discussion

It is important to recall the primary purpose of this Work Package. It was not to generate an exhaustive list of conditions amenable to health care. Rather it was to identify conditions that can be linked to a specific intervention that can be expected to reduce mortality by 30% or more, so that the timing of introduction of this intervention and any effect on mortality can then be examined in a range of European countries. Therefore, no previous lists of 'amenable mortality' were used to operationalise our selection process, partly due the lack of consensus on the definition of 'amenable mortality'. Based on the above arguments, the indicators of amenable mortality that were identified in this study were deaths from those conditions where we can identify interventions that can reduce deaths and for which variation in mortality rates (over time or across populations) reflects variation in coverage and quality of health care (preventive or therapeutic services delivered to individuals). To be included in the list, the specified key intervention (or package of interventions) must be shown (by either patient level studies e.g. randomised controlled trial; or population level studies or both) to be capable of reducing the associated mortality from the linked condition by >30%. Furthermore, the intervention should have been introduced post 1970.

2.4 Conclusion

Any list of causes of amenable death is, of necessity, dynamic, reflecting changes in both diseases and the scope to treat them. Variations in diagnostic practices and cause of death coding also impact on international comparisons. However, the aim of projects such as this is to reach a consensus at a particular point in time so enabling robust international comparisons and target setting. Amenable mortality can never be more than an indicator and cannot, on its own, provide definitive evidence of health system performance. Above all, it is important to bear in mind that with evolving diseases and advancement in health care these indicators cannot be set in stone and will undoubtedly change over time.

Table 2.3 Conditions included (evidence of decline in mortality attributable to health care, evidence of effectiveness of interventions on patient level studies, and ability to identify a key intervention)

Condition	Intervention(s)	How much of any decline can be attributed to health care? (What other factors may have been important?)	Evidence from patient-level studies of 30% or more decline in mortality linked to one or more interventions
Human immunodeficiency virus (HIV)	Diagnosis using HIV antibodies: **1985**, USA [30] Anti-retroviral drugs: azidothymidine (AZT) & zidovudine (ZDV) FDA approval **1987** for treatment [31] and **1990** for prevention of AIDS in people HIV positive. Combination of a protease inhibitor (i.e. saquinavir or ritonavir) and two nucleoside (i.e. lamivudine), and non-nucleoside reverse transcriptase inhibitors (i.e. delavirdine) as highly active antiretroviral treatment (HAART) : **1996-1997**[32]	Between 1996 and 1998, HIV-related morbidity and mortality decreased by 60% in the United States[33] National surveillance data in eight US cities showed marked reductions in morbidity and mortality associated with the acquired. Immunodeficiency syndrome (AIDS) amongst 1255 patients having had at least one CD4+ count below 100 cells per cubic millimetre between the years 1994 - 1997. Mortality among these patients declined from 29.4 per 100 person-years in 1995 to 8.8 per 100 person-years in the second quarter of 1997. There were reductions in mortality regardless of sex, race, age, and risk factors for transmission of HIV. Combination antiretroviral therapy was associated with the most benefit; the inclusion of protease inhibitors in such regimens conferred additional benefit. Patients with private insurance were more often prescribed protease inhibitors and had lower mortality rates than those insured by Medicare or Medicaid[34]. In an observational study of 8556 HIV-positive patients death rates declined from 15.6 to 2.7 per 100 person-years of follow-up (PYFU) between 1994 and 2001. Pre-AIDS incidence declined from 2.4 to 1.1 per 100 PYFU. The ratio of overall to pre-AIDS deaths peaked in 1996 at 8.4 and dropped to < 3 after 1998. The adjusted odds of dying following one AIDS defining event (ADE) increased yearly (odds ratio, 1.53; P < 0.001), conversely the odds of dying following three or more ADE decreased yearly (odds ratio, 0.79; P < 0.001). The proportion of deaths that followed an HIV-related disease decreased by 23% annually; in contrast there was a 32% yearly increase in the proportion of deaths due to known causes other than HIV-related or suicides. Injecting drug users (IDU) were significantly more likely to die before an ADE than homosexuals (relative hazard, 2.97; P < 0.0001) and patients from northern/eastern Europe (relative hazard, 2.01; P < 0.0001) were more likely to die pre-AIDS than southern patients. The proportion of pre-AIDS deaths increased from 1994 to 2001; however, the incidence of pre-AIDS deaths and deaths overall declined. IDU and subjects from northern/eastern Europe had an increased risk of pre-AIDS death. HIV-positive patients live longer therefore it is essential to continue to monitor all causes of mortality to identify changes[35].	The first major study of efficacy of AZT was a RCT in patients with either AIDS diagnosed by the presence of Pneumocystis carinii pneumonia alone, or with what was then termed advanced AIDS-related complex. Follow up was between 8 and 24 weeks. Mortality among those receiving AZT was 1/145 (<1%) and among controls was 19/137 (14%) while all intermediate measures (opportunistic infections, CD4 counts) were significantly better in the intervention group [36]
Score		3	4
Commentary: The **key intervention** was AZT, in the late **1980**s. An initial small RCT, where the main end points were intermediate outcomes, nonetheless reported a 95% reduction in mortality over up to 24 weeks. Subsequent observational data confirmed the ability to achieve sustained and substantial reductions in mortality. However, resistance emerged to the initial drugs, such as AZT. Subsequent improvements in mortality at a population level probably reflect a combination of therapeutic advances and improved understanding of the management of AIDS and the opportunistic infections that accompany it. Overall, the available evidence suggests a major impact of treatment on mortality during the early 1990s.			

Condition	Intervention(s)	How much of any decline can be attributed to health care? (What other factors may have been important?)	Evidence from patient-level studies of 30% or more decline in mortality linked to one or more interventions
Malignant neoplasm of rectum, rectosigmoid junction and anus & colon	Surgery : early **1970**s CT colonoscopy and flexible sigmoidoscopy mid **1990**s[37] Chemotherapy: oxaliplatin (UK: licensed **1999** for the first line treatment of metastatic colorectal cancer in combination with 5-fluorouracil and folinic acid) [38;39] Colorectal cancer screening[40;41] (Targeted programmes in the UK from **2006** (England: **2006**; Scotland: **2007**; Wales: **2008**))	Data for patients diagnosed in 1995-1999 and followed to 2003, reported that the mean Europe age-standardised five-year relative survival was marginally higher for colon cancer (55%) than for rectal cancer (53%). With women having better survival than men for both colon and rectal cancers[42]. The first EUROCARE study showed that for patients diagnosed in 1978-1989 five year survival improved, from 40 to 48% for colon cancer and 38 to 46% for rectal cancer. There was considerable variation among countries (high in the Nordic countries (Denmark excluded), The Netherlands, Switzerland, France and Austria and low in Eastern European countries, the U.K. and Denmark. It is believed that inter country and time differences in survival differences are related to stage at diagnosis and postoperative mortality[18]. Further gains were reported in the most recent EUROCARE II study, with rectal cancer improving from 45% in 1988–1990 to 55% in 1997–1999. Results for rectal cancer were similar to those for colon cancer[43] Mortality from colorectal cancer in the EU has been declining from 13.4 to 11.5/100 000 from 1980–1984 to 2000–2004 in women and from 20.1 to 18.8/100 000 from 1990–1994 to 2000–2004 in men. These falls were somewhat larger in middle age. The favourable trends in colorectal cancer mortality were observed in most western and northern Europe, whereas trends were less favourable in southern (particularly Spain) and most central and eastern European countries, which had lower mortality rates in the past [11].	The addition of chemotherapy to patients following curative resection seems to confer a small survival benefit. 3239 patients (2963 [91%] with stage II [node negative] disease, 2291 [71%] with colon cancer from 150 centres in 19 countries were randomly assigned to receive chemotherapy with fluorouracil and folinic acid or to observation (with chemotherapy considered on recurrence). Chemotherapy was delivered as six 5-day courses every 4 weeks or as 30 once-weekly courses of intravenous fluorouracil (370 mg/m2) with high-dose (175 mg) L-folinic acid or low-dose (25 mg) L-folinic acid. Until 1997, levamisole (12 courses of 450 mg over 3 days repeated every 2 weeks) or placebo was added. After 1997, patients who were assigned to receive chemotherapy were given fluorouracil and low-dose folinic acid only. After a median follow-up of 5.5 (range 0-10.6) years, there were 311 deaths in the chemotherapy group and 370 in the observation group; the relative risk of death from any cause with chemotherapy versus observation alone was 0.82 (95% CI 0.70-0.95; p=0.008)[44]. Faecal-occult-blood (FOB) screening undertaken in an unselected population-based randomised controlled; 1981 - 1991, 152,850 people aged 45-74 years who lived in the Nottingham area of the UK. The incidence of cancer in the control group (856 cases, 11% stage A) was 1.44 per 1000 person-years. Median follow-up was 7.8 years (range 4.5-14.5). 360 people died from CRC in the screening group compared with 420 in the control group-a 15% reduction in cumulative CRC mortality in the screening group (odds ratio=0.85 [95%; CI 0.74-0.98], p = 0.026)) [45] RCTs examining surgical treatment of colo-rectal cancer have largely compared open and laparoscopic methods, finding little difference in outcome.
Score		3	1
Commentary: Colorectal cancer is universally fatal if untreated. Some cases will have been cured once intra-abdominal surgery became possible in the late 19th century but reliable population-based 5-year survival figures are only available from the 1970s, when they were about 40%. In the highest performing health systems they are now around 60%, a 50% improvement. As with many other cancers it is not possible to attribute this improvement to a single **key intervention**. Rather it seems to have been a combination of earlier diagnosis (FOB screening, sigmoid/ colonoscopy), improved surgical and anaesthetic technique (with reduced peri-operative mortality), and the more recent introduction of chemotherapy. It can be expected that countries implementing population-based screening will achieve further improvements, although inevitably, this will create difficulties in assessing survival due to the introduction of lead time bias.			

Condition	Intervention(s)	How much of any decline can be attributed to health care? (What other factors may have been important?)	Evidence from patient-level studies of 30% or more decline in mortality linked to one or more interventions
Malignant neoplasm of cervix uteri	Cytological examinations **1941** (George Papanicolaou) Pap test screening **1950** Screening programmes early **1970**s (UK: organised public screening introduced in **1988**[46]) Diagnostic testing early **1990**s Diagnostic testing: colposcopy Large loop excision of the transformation zone (LLETZ) Cone biopsy Further tests: Examination under anaesthetic, Magnetic Resonance Imaging (MRI), CT, Pelvic ultrasound Radiotherapy; Chemotherapy & Surgery HPV vaccination from early **2000**s	Sweden, having a nationwide programme of cervical screening, saw a reduction in mortality from cervical cancer of 50% in 1965-1982. Denmark, whose organised programmes covered 40% of the population, saw a reduction of 25%, while Norway, where only 5% of the population were covered, mortality fell by only 10%[47]. In the United Kingdom, with no comprehensive screening. Programme at the time, saw a decrease of only 7% between 1974 and 1982 [48;49]. The EUROCARE II study did not document a significant increase in survival of women with established cancer of the cervix, after accounting for lead time bias due to screening. Mean age and area-adjusted five-year relative survival in Europe was 63%. [42] Survival for cervical cancer was significantly higher than the European mean in northern Europe and Switzerland, and significantly lower in Poland, in Portugal and in England and Wales[43]. Cervical cancer incidence fell by 42 per cent between 1988 and 1997 (England and Wales). This fall has been attributed to the cervical screening programme. [50] There was a 25 per cent decrease in the incidence rate of cervical cancer for women under the age of 70 from 1990 to 1992. This has been attributed to a rapid increase in coverage of the cervical screening programme which occurred from 1989 onwards. [51] In several of the European countries it is difficult to distinguish, on the basis of death certification, cervical and endometrial cancer, but the trends in uterine cancer mortality have likely been affected mostly by the fall in cervical cancer reports La Vecchia et al (2009). The long-term decline in (cervix) uterine cancer mortality has continued over the last decade (from 1990–1994 and 2000–2004), with a fall from 7.1 to 5.7/100 000 (–19%) in overall mortality rates, and from 12.5 to 10.1/100 000 (–19%) at age 35–64 years. This is essentially due to a wider adoption of cervical screening programmes in western and northern Europe[11].	Five randomised trials of concurrent chemo-irradiation for patients with locally advanced cervical cancer in 1999 and 2000 showed that overall survival and recurrence was reduced by 50%. Following this revelation the National Cancer Institute issued a Clinical Alert advising that concurrent chemotherapy (typically, single-agent cisplatin) be incorporated into the treatment program of women scheduled to receive definitive pelvic radiotherapy. Although the adoption of this new standard has been linked to improved overall survival the prognosis is very poor and, ultimately, therapy in this setting is palliative in nature[52].
Score:		2	3
Commentary: The **key intervention** is cervical screening. However, it is difficult to add a precise date as it was often introduced on an opportunistic basis, often missing those at greatest risk. It is also difficult to ascertain how much of the observed decline in mortality can be attributed to screening because of changing incidence. Nonetheless, where population -based screening programmes exist, a substantial reduction in mortality has been achieved. Much of this is due to the detection and treatment of pre-malignant lesions. There is little evidence to suggest that new treatments for invasive cervical cancer are having a significant effect at a population leve.l			

Condition	Intervention(s)	How much of any decline can be attributed to health care? (What other factors may have been important?)	Evidence from patient-level studies of 30% or more decline in mortality linked to one or more interventions
Malignant neoplasm of the testis	Surgery early **1970**s Diagnostic testing surgery; chemotherapy; radiotherapy Chemotherapy Mid **1970**s :cisplatin – approved by FDA **1978**[53] (UK: cisplatin approved in **1979**[54]	Testicular cancer has a peak incidence at around 30 years of age, and it is the most common cancer in men under 35 years of age, accounting for a third of all cancers in that age range. The age distribution is unusual among adult malignancies, with almost 70% of cases arising in men under 40 years of age, and only about 2% in men over 70 years of age. Incidence has increased steadily in many developed countries over the last 50 years, including the United Kingdom. In men under 50 years of age, incidence has risen almost two-fold in England and Wales in the last 30 years, but the increase has been much smaller among older men. For men diagnosed during 1986–1990, relative survival was 96% at 1 year after diagnosis and 91% at both 5 and 10 years. Survival has risen further with time, so that for men diagnosed during 1996–1999, relative survival had reached 98% at 1 year after diagnosis and 97% at 5 years. Ten-year survival was effectively the same as 5-year survival. If the most recently observed survival patterns were to persist unchanged for the rest of the decade, men diagnosed in the first few years of the 21st century may expect 10-year relative survival rates that approach 96%. Survival rose substantially for older men during the 1990s, and the huge decline in survival with age became less marked. Thus, 5-year relative survival was over 90% for men diagnosed under the age of 50 during the decade 1986–1995, but less than 70% for men aged 70–79 years, and less than 40% for elderly men (80–99 years). For men aged 80–99 years diagnosed during 1996–1999, however, 5-year survival had risen to 55%[55]. Inter-country differences in survival in patients aged 15-44 years at diagnosis, 1-year relative survival rates between 95 and 100%, and 5-year rates between 90 and 95% were observed in most participating countries of Northern, Western, Central and Southern Europe, and the U.K. Five-year rates under 90% were seen for France (87%), Slovenia (88%), Slovakia (82%), Poland (83%) and Estonia (51%). Age-standardised 1-year rates of 95% or higher and 5-year rates of 89% or higher were revealed for Finland, Sweden, Denmark, the U.K., Germany, Switzerland, Spain and Italy. In Eastern Europe, the 1-year rate ranged from 68% (Estonia) to 93% (Slovenia) and the 5-year rate ranged from 48% (Estonia) to 84% (Slovenia). Relative survival generally decreased with increasing age of patients. The 5-year relative survival rate, based on the weighted analysis of pooled European data, was 91% for patients aged 15-44 years, 85% for patients aged 55-64 years and 59% for patients aged 75 or over[12]. Testicular cancer mortality has steadily declined in the EU from 1990–1994 to 2000–2004, from 0.47 to 0.35/100 000 (–26%) at all ages and from 0.59 to 0.46/100 000 (–22%) at age 35–64[11].	Testicular cancers are divided into seminomas, making up about half of all testicular tumours and occur in older patients; and non-seminomatous tumours, comprising teratomas, mixed tumours, and other cell types, which tend to occur in younger patients. Several staging systems for testicular cancer have been developed; most commonly used system in current practice is the International Germ Cell Consensus Classification, which classifies testicular tumours as good prognosis, intermediate prognosis, or poor prognosis. 90% of seminomas are classified as good prognosis. A systematic review, in relation to relapse rates, response rates and mortality aimed to answer the effects of treatments in men: With stage 1 seminoma (confined to testis) who have undergone orchidectomy? With good-prognosis non-stage 1 seminoma who have undergone orchidectomy? The effects of maintenance chemotherapy in men in remission after orchidectomy and chemotherapy for good-prognosis non-stage 1 seminoma? The effects of treatments in men with intermediate-prognosis seminoma who have undergone orchidectomy? **Mortality :** Etoposide plus cisplatin compared with etoposide plus carboplatin Etoposide plus cisplatin may increase relapsefree survival rates at about 2 years (but not overall survival rates) in men with good-prognosis non-stage 1 seminoma, teratoma, or mixed tumours compared with etoposide plus carboplatin (low-quality evidence). Etoposide plus cisplatin plus bleomycin compared with etoposide plus cisplatin Etoposide plus cisplatin plus bleomycin may increase survival rates at 3 years in men with good-prognosis non-stage 1 seminoma, teratoma, or mixed tumours compared with etoposide plus cisplatin (very low-quality evidence). Two-drug compared with five-drug regimen Etoposide plus cisplatin may not increase overall survival rates at 5 years in men with good-prognosis non-stage 1 seminoma, teratoma, or mixed tumours, but may reduce toxicity, compared with a five-drug regimen of cisplatin, vinblastine, bleomycin, cyclophosphamide and dactinomycin (very low-quality evidence). Bleomycin plus vinblastine plus cisplatin compared with cisplatin plus vinbastine Adding bleomycin to two-drug regimens containing vinblastine plus cisplatin reduces tumour-related mortality at 4 years in men with non-stage 1 goodprognosis tumours compared with vinblastin plus cisplatin (moderate-quality evidence. Three cycles compared with four cyclesWe don't know whether three cycles of chemotherapy may increase progression- free or overall survival rates in men with both seminomas and non-seminomas compared with four cycles, but three cycles may be more effective at reducing toxicity (low-quality evidence. Single-agent compared with combined chemotherapy Single-agent carboplatin may not reduce mortality rates at 52 months to 3 years compared with combined chemotherapy regimens (low-quality evidence)[56].
Score		3	2
Commentary: Dramatic improvements in survival rates have resulted, from advances in combination chemotherapy i.e. introduction of cisplatin and , the use of more effective imaging techniques, the introduction of appropriate serum markers which allow for careful follow-up, and the modification of surgical techniques. Although there is considerable suggestive evidence implicating the introduction of cisplatin in improved survival, the combination of developments at the time it was being introduced make it difficult to quantify its effect on mortality with certainty.			

Condition	Intervention(s)	How much of any decline can be attributed to health care? (What other factors may have been important?)	Evidence from patient-level studies of 30% or more decline in mortality linked to one or more interventions
Hodgkin's disease	Combined key interventions; Chemotherapy; Nitrogen Mustard **1922** and Radiotherapy **1902**[57;58] . Combination chemotherapy **1970s**[59] High dose therapy and peripheral blood stem cell transplantation: Late **1990s** [60]	Five-year relative survival rate for Hodgkin's disease between 1940 to 1964 improved from 24 to 41% [61]. Age-adjusted rates, based on the world standard population and age-adjusted death rates of Hodgkin's disease (HD) for men and women in 19 European countries besides the EU, USA and Japan in 1965–69 and 1995–98 showed that in most western European countries, rates fell by 70–80%. However, the decline in HD mortality for men aged 15 to 44 was -79% in the EU, -77% (in the USA, and -82% in Japan. Corresponding values for women were -79% in the EU, -75% in the USA, and -80% in Japan [62]. Mortality from Hodgkin lymphomas continued to decline across Europe. From 1990–1994 to 2000–2004, in the EU as a whole, the fall was from 0.82 to 0.49/100 000 (–40%) in men and from 0.48 to 0.31/100 000 (–35%) in women. In both sexes, the falls approached 50% in young and middle age[11].	More than 80% of younger people with early stage Hodgkin's lymphoma and 60–70% of people with advanced stage Hodgkin's lymphoma are cured. There is no evidence that radiotherapy and chemotherapy combined improves overall survival in people with early or intermediate stage Hodgkin's lymphoma, compared with radiotherapy alone. There is conflicting evidence on the effect of additional radiotherapy on overall survival compared with combination chemotherapy regimens in people with advanced Hodgkin's lymphoma. Optimal doses and volume of radiotherapy after chemotherapy have yet to be determined. Two meta-analyses and 12 randomised controlled trials (RCTs) (2010 people) were identified. *Early (stage I and II) and intermediate stages (stage I and II with other prognostic factors):* One meta-analysis and one RCT found no difference in overall survival among different radiotherapy doses or regimens. One meta-analysis and 7 RCTs found no difference in overall survival among different chemotherapy regimens plus radiotherapy compared with radiotherapy alone (High study quality only 79% vs. 77%). *Advanced stages (stage III and IV):* One meta-analysis and one moderate quality RCT found that overall survival was significantly improved with combination chemotherapy regimens compared with chemotherapy plus radiotherapy. The same meta-analysis and three subsequent RCTs found no significant difference in overall survival between chemotherapy alone and chemotherapy plus radiotherapy (High study quality only no difference) [63].
Score		3	4
Commentary: The **key intervention** is combined chemo- and radiotherapy, introduced in the 1940s, when survival rates of 40% were already being achieved with rudimentary regimes. Since then, a series of advances in treatment, including the introduction of new therapeutic entities and improved management of the disease process and its complications have approximately doubled the survival rate, although international differences remain.			

Condition	Intervention(s)	How much of any decline can be attributed to health care? (What other factors may have been important?)	Evidence from patient-level studies of 30% or more decline in mortality linked to one or more interventions
Rheumatic heart disease	Antibiotics:**1940**s Heart valve surgery: closed mitral valvotomy **1925** Tuffier **(1914)** performed the first recorded aortic valvotomy in which he dilated the valve digitally, Brock **(1954)** split the stenosed aortic valve with a tenotome or dilator, and the dramatic work of Hufnagel and Harvey **(1953)** subsequently led to valve replacement by prosthesis (Starr and Edwards1961)[64] (UK); mitral valve repair attempted **1951/2** but abandoned until **1970**s.	Rheumatic fever is common worldwide and responsible for many cases of damaged heart valves. In Western countries, it became fairly rare since the 1960s, probably due to widespread use of antibiotics to treat streptococcus infections. Rheumatic fever primarily affects children between ages 5 and 15 years and occurs approximately 20 days after strep throat or scarlet fever. In up to a third of cases, the underlying strep infection may not have caused any symptoms. The rate of development of rheumatic fever in individuals with untreated strep infection is estimated to be 3%. The rate of development is far lower in individuals who have received antibiotic treatment. Persons who have suffered a case of rheumatic fever have a tendency to develop flare-ups with repeated strep infections. The recurrence of rheumatic fever is relatively common in the absence of maintenance of low dose antibiotics, especially during the first three to five years after the first episode. Heart complications may be long-term and severe, particularly if valves are involved. A review of the medical literature revealed that the incidence of rheumatic fever has been declining for at least 150 years, preceding by many decades the use of penicillin as a preventive measure. Simultaneously, the prevalence of rheumatic heart disease has diminished. Streptococcal upper respiratory tract infections remain common but with reduced severity and fewer subsequent cases of rheumatic fever. There has been a marked decline in mortality due to rheumatic fever in the United States. Evidence for the important role of penicillin in changing the severity of rheumatic carditis started around 1946. Since then, mortality due to rheumatic carditis has rapidly decreased. A hospital based study revealed the rate of loss of all murmurs amongst the inpatients accelerated exceeding 40 percent by 1970, and the rates of decline in national mortality due to rheumatic carditis accelerated fourfold with the advent of antibiotics[65].	Not all treatments for rheumatic fever have been tested in randomised controlled trials. Some are based on anecdotal evidence, common sense, and proven safety. For example, penicillin is considered mandatory for the eradication of possibly persistent group A streptococcus infection of the upper respiratory tract, though this treatment has not been shown to alter the cardiac outcome after 1 year in controlled studies. Similarly, long-term bed rest accelerated recovery from carditis and reduced the incidence of relapse before penicillin was available, but since its emergence no randomised studies have been done. Although most patients with rheumatic fever need bed rest early in their illness. Results of a randomised controlled trial showed that patients treated with aspirin for 12 weeks had a similar prevalence of murmurs 1 year later as did untreated controls. Findings of meta-analyses indicate no benefit of salicylates over corticosteroids or vice-versa in reducing the subsequent development of rheumatic heart disease. Corticosteroids greatly reduce the inflammatory response of active rheumatic fever, especially fever and raised concentrations of acute phase reactants. Results of randomised trials done before echocardiography became available and those of subsequent meta-analyses have not shown a benefit of corticosteroids over placebo or salicylates in the prevalence of residual rheumatic heart disease in the 1–10 years after rheumatic fever. However, all of the studies included in these meta-analyses were done more than 40 years ago, before echocardiography, and most did not test corticosteroids that are in common use today. In a placebo-controlled, randomised trial, intravenous immunoglobulin administered to patients with rheumatic fever early after presentation did not alter the clinical course or lead to reduction in echocardiographic evidence of acute valvular disease or chronic cardiac damage at 1 year. With echocardiography, results of a follow-up study 6 months to 7 years after the first episode of rheumatic fever indicated that 64% of patients with carditis had evidence of improvement, and that murmurs disappeared at follow-up in 41% of those with mild carditis, 36% with moderate carditis, and 24% with severe carditis initially cited in Carapetis et al, 2005.[66]
Score		1	2
Commentary: The **key intervention** in treatment of established disease is valve surgery, with progressive enhancements since the 1950s, while **antibiotics** have been key in preventing onset of disease. Over the past century, as living conditions have become more hygienic and less crowded, and nutrition and access to medical care have improved, active rheumatic fever and rheumatic heart disease have become rare in developed countries. The introduction of antibiotics has also helped to reduce the burden of disease, though to a lesser extent than these other factors.			

Condition	Intervention(s)	How much of any decline can be attributed to health care? (What other factors may have been important?)	Evidence from patient-level studies of 30% or more decline in mortality linked to one or more interventions
Hypertension	**1930**s veratrum alkaloids orally and parenterally **1940**s ganglion blocking agents Thiazide diuretics from the mid-**1960**s[67;68] followed progressively by beta blockers, ACE inhibitors, and calcium antagonists.	A retrospective US study between the late 1960s and late 1980s assessed the changes in prevalence, treatment, and control status of hypertension in an elderly population; aged ≥65 years. The overall prevalence of HBP amongst this group showed a gradual but statistically significant decline, from 51% to 44% between 1967 and 1988. The trend toward increased percent on treatment and controlled, compared with those uncontrolled with or without treatment, was significant among all age-sex groups except males aged over 75years. The hypertensives on treatment in the 1967 sample were being managed with diuretic medications. By 1988, diuretic use had dropped to 73% and peripheral adrenergic antagonist use to 1% Beta blockers, introduced in the mid-1970s, and ACE inhibitors and calcium antagonists (CAs), introduced in the 198Os, showed Increasing frequency of use among treated hypertensives in the 1981 and1988 survey subjects. Proportion of hypertensives being managed with one, two, or three drugs remained the same [69].	The very first large long term clinical trials examined antihypertensive treatment effectiveness in reducing cardiovascular morbidity and mortality in patients with mild hypertension. The results these studies have provided the basis upon which major conclusions being drawn in relation to the therapy of mild to moderate hypertension. Of these studies only the Veterans Administration and the Oslo trials used male subjects only [8]. Since such trials, beta-blockers were widely accepted as the first line treatment therapy for hypertension. A review conducted by Wiysonge et al (2007) looked at the effectiveness of betablockers, compared to other classes of drug in the treatment of hypertension. They review a total of 13 RCTs (N=91,561 participants), comparing beta-blockers to placebo or no treatment (4 trials with 23,613 participants), diuretics (5 trials with 18,241 participants), calcium-channel blockers (CCBs: 4 trials with 44,825 participants), and renin-angiotensin system (RAS) inhibitors (3 trials with 10,828 participants). The risk of all-cause mortality was not different between first-line beta-blockers and placebo. The available evidence did not support the use of beta-blockers as first-line drugs in the treatment of hypertension. They based this conclusion on the relatively weak effect of beta-blockers to reduce stroke and the absence of an effect on coronary heart disease when compared to placebo or no treatment. Also, it is based on the trend towards worse outcomes in comparison with calcium channel blockers, renin-angiotensin system inhibitors, and thiazide diuretics [70].
Score		2	3
Commentary: The **key intervention** was the introduction of safe antihypertensive drugs with few side effects, in the 1960s. However, since then, gains can be attributed to a progressive expansion of those considered eligible for treatment (to older patients and those with lower initial blood pressure), a process facilitated by the development of drugs with fewer side effects.			

Condition	Intervention(s)	How much of any decline can be attributed to health care? (What other factors may have been important?)	Evidence from patient-level studies of 30% or more decline in mortality linked to one or more interventions
Ischaemic heart disease (IHD)	Diagnosis using cardiac enzyme levels; electrocardiogram; cardiac stress testing; coronary angiograms (before **1960**s) Betablockers (for secondary prevention of myocardial infarction after above studies[71;72]): **1980**s, USA : • Pindolol (FDA approval **1982**) [71;73] • Propranolol (FDA approval **1983**) • Acebutolol (FDA approval **1984**) Antiplatelets; lipid lowering statins ACE inhibitors; thrombolytics/fibrinolytis; antiplatelets and anticoagulant Percutaneous coronary interventions; stents, coronary angioplasty Surgery: coronary artery bypass grafting (CABG)	From 1980-2000, several international studies have reported that in addition to changes in known risk factors, some of the decline observed in ischaemic heart disease mortality was attributable to treatment. Covering time periods between the years 1974-2000, these studies used mainly the IMPACT or cohort models of mortality looking at both risk factors and treatment effects. Collectively, these percentage declines ranged from the lowest in Finland: 23% and the highest observed in the USA: 47%[74-83].	Coronary care units: A RCT published in 1976 compared outcome in men with an acute myocardial infarction allocated either to home care or admission to an intensive care unit. Mortality was slightly higher in those admitted to an intensive care unit.[84] Clearly, the scope of treatment available now is vastly different from that in the early 1970s but it remains the case that the benefits of admission to a coronary care unit remain unproven in RCTs. Trials of secondary prevention: Three trials similar in design, used different beta blockers–timolol, metoprolol and propranolol. Patients were recruited at the time of hospitalization for their acute infarct and then followed up on medication an average of three months for metoprolol, 17 months for timolol and 25 months for propranolol. Collectively, these trials revealed that the regular oral use of these beta blockers after acute myocardial infarction resulted in a significant reduction in total mortality, averaging about 35% at one year with evidence of continued effect as long as three years after infarct. These different beta blockers were found to be equally useful, as the observed effect seemed to be due to a class action due to beta blockade, a property shared by all these drugs. However, these trials left unanswered the question of the value of therapy initiated after the immediate postinfarct period as well as the duration of benefit in long-term treatment[85]. From1974 -1982, nine randomised trials, including 11485 survivors of myocardial infarction, of placebo controlled and double-blind effects of betablockers have been reviewed. Of these studies, two confirmed that betablockers prolong life in post-Ml patients[86].
Score		2	4
Commentary: Available evidence suggests that improvements in diet with concomitant declines in serum cholesterol concentration, decreased cigarette smoking, improved hypertension control, and possibly increased leisure-time physical exercise explain a portion of the mortality decline. Coronary care units may have contributed [87] (the potential to intervene in the early CCUs, when the first RCT was undertaken, was much less than now) and therefore it is difficult to ascertain a **key intervention**.			

Condition	Intervention(s)	How much of any decline can be attributed to health care? (What other factors may have been important?)	Evidence from patient-level studies of 30% or more decline in mortality linked to one or more interventions
Heart failure	Digitalis Preparations; **1780s** Digoxin; digitoxin Diuretics: late 1950s; hydrochlorothiazide, FDA approval **1959** Angiotensin converting enzyme (ACE) inhibitors; captopril FDA approval **1981**; enalapril FDA approval **1983**	Historical: It was not until 1542 that the German scholar Fuchsius coined the now common term digitalis for the foxglove plant. Since 1785, when Sir William Withering published his textbook on the "account of the foxglove," physicians have used digitalis preparations to treat edematous states, atrial fibrillation, and chronic heart failure (HF). Withering reported that digitalis slowed heart rate in patients with an irregular pulse and result in dieresis. Two studies looked at the contribution of heart failure to overall mortality. The first of which looked retrospectively at death certificates in Scotland during 1979-1992. Mortality rates for heart failure, standardised by age and sex fell by 31% in men and 41% in women <65 years during this period[88]. The second study showed that the population impact of newer therapies for heart failure. Looking at the survival of patients hospitalised for heart failure in Scotland during 19861995. After adjustment, 30 day case fatality rates fell between 1986 and 1995 by 26% in men and 17% in women. This was the first UK study to look at survival in unselected patients.[89]	The ability to diagnose heart failure (and specifically to differentiate it from other causes of dyspnoea) has improved considerably with the advent of echocardiography (in the early 1980s) and, since about 2000, the use of atrial natriuretic peptide. [90]The initial phase III trials of diuretics did not include mortality as an end point and, in most cases, assessed their potential in reducing blood pressure. A systematic review of a number of small randomised trials indicated a possible benefit from diuretics in terms of mortality, compared to placebo. [91] Although widely used for many decades, controversy persisted about the ability of treatment with digitalis to reduce mortality in patients with heart failure. This was addressed in a Cochrane systematic review which included 13 randomized controlled trials (RCTs) (n = 7896); however, the majority of the effect on mortality and hospitalizations was due to one trial (the Digitalis Investigation Group [DIG]) trial. [92] Eight RCTs examined mortality; n = 7755): There was no evidence of a significant difference in mortality between the digitalis treatment and control groups (odds ratio [OR] 0.98, 95% CI 0.89 to 1.09). The DIG trial was an RCT (n = 6800) comparing digoxin with placebo for the treatment of people with heart failure in sinus rhythm. Trial participants were allowed to take other heart failure treatments, and most were taking ACE inhibitors and diuretics. Mean follow up was 37 months: All-cause mortality did not differ between the digoxin and placebo groups (34.8% compared to 35.1%; RR 0.99, 95% CI 0.91 to 1.07). Cardiovascular death rate did not differ between the digoxin and placebo groups (29.9% compared to 29.5%; RR 1.01, 95% CI 0.93 to 1.10). Fewer hospitalizations due to worsening heart failure occurred in the digoxin group than the placebo group (26.8% compared to 34.7%; RR 0.72, 95% CI 0.66 to 0.79). The benefit of digoxin seemed to be greater among people at highest risk (lower ejection fractions, enlarged hearts, and severe symptoms)[93]. A systematic review of five trials found that ACE-inhibitors significantly reduced the number of deaths compared with placebo. Overall 12 763 patients were randomly assigned treatment or placebo and followed up for an average of 35 months. Overall, the rate of death was 23.0% in the ACE inhibitor group and 26.8% in the placebo group (16% improvement in survival) with the benefits being observed early after the start of therapy and persisting long term. The benefits of treatment on all outcomes were independent of age, sex, and baseline use of diuretics, aspirin, and ß-blockers. Although there was a trend towards greater reduction in risk of death or readmission for heart failure in patients with lower ejection fractions, benefit was apparent over the range examined. This review showed that ACE inhibitors lower the rates of mortality, myocardial infarction, and hospital admission for heart failure in patients with left-ventricular dysfunction or heart failure with or without a recent myocardial infarct.[94]
Score		2	1
Commentary: None of the therapeutic interventions has been shown to reduce mortality by >30%. However, interpretation of the findings from RCTs is complicated as control groups are invariably on some form of medication. Nonetheless, ACE inhibitors do seem to have a substantial incremental benefit, especially when coupled with improved recognition and more ambitious treatment.			

Condition	Intervention(s)	How much of any decline can be attributed to health care? (What other factors may have been important?)	Evidence from patient-level studies of 30% or more decline in mortality linked to one or more interventions
Stroke /Cerebrovascular Disease	Antihypertensive treatment from the mid-**1960**s[67;95] Intensive Management of acute stroke: CT scan & thrombolytic therapy from the mid-**1990**s	Stroke mortality in the United States has declined since 1900. The mortality rates from stroke in Rochester, Minnesota, compared to US white population mortality rates have declined 76% since 1950, and the primary cause for the declines is a decrease in the incidence of new cases of cerebral infarction and cerebral haemorrhage. There are no data on the incidence of stroke prior to 1945 to confirm the US mortality trend. The decline in incidence was noted in women 10- 15 years before it was seen in men. Hypertension is the most important risk factor for stroke. Hypertension surveys have shown an increasing effectiveness of antihypertensive medication in lowering blood pressure, and the effect was noted earlier in women. Available evidence is consistent with the idea that treatment of hypertension is the only significant contributor to the decline of stroke[95]. A retrospective US study looked at the decline in stroke mortality among older persons; aged ≥65 years between 1967 and 1985. It explored the competing explanatory mechanisms of decreased incidence of stroke versus decreased case-fatality rate. It found no significant change in stroke incidence over time; but one month case fatality declined from 33% in 1967 through 1971 to 18% in 1981 through 1985; median survival increased from 213 to 1092 days. Indices of reduced severity included declines in coma from 27% to 12% and in wheelchair- or bed-bound status from 40% to 30%, concluding that in this well-defined older population, stroke has become a less lethal and disabling though no less common disease [96]. The Oxford Record Linkage Study contains data from 1979 to 2004 while there are also English national data from 1996 to 2004. Mortality rates based on underlying cause and based on all mentions showed similar downward trends. Mortality based on underlying cause alone misses about one quarter of all stroke-related deaths. Changes during the period in the national rules for selecting the underlying cause of death had a significant but fairly small effect on the trend. Overall, mortality fell by an average annual rate of 2.3% (95% confidence interval 2.1% to 2.5%) for stroke excluding subarachnoid haemorrhage; and by 2.1% (1.7% to 2.6%) per annum for subarachnoid haemorrhage. Stroke mortality in the Oxford region halved between 1979 and 2004[97].	No single intervention has shown a reduction in mortality of 30% or more. Early studies of the effect of antihypertensives in hypertension showed that they reduced deaths from stroke[6-10]. National guidelines recommend the treatment of hypertension to prevent stroke. The Quality and Outcomes Framework, which is a scheme for paying primary care physicians for providing high quality care, includes a series of measures related to hypertension. These include: BP 4.The percentage of patients with hypertension in which there is a record of the blood pressure in the past 9 months BP 5. The percentage of patients with hypertension in whom the last blood pressure (measured in last 9 months) is 150/90 or less These data are available at practice level: http://www.qof.ic.nhs.uk/[98]
Score		3	1
Commentary: Treatment of hypertension is the **key intervention** in reducing stroke incidence. Although the evidence is largely circumstantial, it seems likely that this is the main explanation for the reduction of stroke mortality of about two-thirds. The most important development was not the discovery of antihypertensive but rather the publications of studies in the 1960s showing that control of essential hypertension would reduce the incidence of stroke. There is limited evidence that treatment of established stroke by, for example, thrombolytic therapy in patients with occlusive stroke or surgical treatment of aneurysms in patients suffering from subarachnoid haemorrhage has made a significant impact on population level mortality.			

Condition	Intervention(s)	How much of any decline can be attributed to health care? (What other factors may have been important?)	Evidence from patient-level studies of 30% or more decline in mortality linked to one or more interventions
Peptic ulcer	Surgery from the **1890**s H2-receptor-antagonists in the late **1970**s (cimetidine (Tagamet)[99-101]. First marketed in UK in **1976**. Laparoscopic management **2000** [102;103] Acute or chronic (medication - H2 blockers or proton pump inhibitors) Diagnostic testing of H pylori (antibiotics plus above); Gastroscopy, Endoscopy	An age-period-cohort analysis (age range 25-79) undertaken used death rates from peptic ulcer between 1955 and 1989 in 24 European countries. In the late 1950s, the range of variation of the world standardized rates was between 4/100 000 in France and 17.8 in Portugal. In the late 1980s, only Ireland had a rate over 5/100 000, and values for most Western countries ranged between 2 and 4/100 000. The average fall in rates over the last three decades was 56%. Of this, a high proportion (45%) was registered between 1975 and 1984. In Eastern Europe, no systematic change was observed until the early 1970s, but over the last 15 years peptic ulcer mortality declined by an average of 20%. In 1985–1989 the lowest rate was 4.5/100 000 in Bulgaria, and for all other countries peptic ulcer mortality ranged between 5 and 7.2/100 000. Peptic ulcer mortality was substantially lower in females, and showed no appreciable modification in Western Europe and several increases in Eastern Europe until the mid 1970s. Thereafter, mortality declined by an overall 25% in the West and 15% in the East. Earlier declines for males in Western Europe were chiefly related to a cohort effect*. The recent falls, in contrast, were mainly period effects indicating a contribution of therapeutic advancements (including the introduction of H_2-receptor-antagonists in the mid-1970s) [101]. *Cohort values related to earlier and more recent periods are based on fewer age-specific rates (e.g. only one for the 1885 cohort, two for 1890, etc.) and hence are less stable and reliable than central ones. Earlier declines for males in Western countries were chiefly related to a cohort effect, since rates had started to decline from younger generations. This probably reflects more favourable patterns of exposure to risk factors for ulcer (such as diet, *Helicobacter pylori* or other infectious agents, and smoking). These downward trends were not observed in Eastern European countries, whose fall in cohort values were later and more moderate, and whose rates did not appreciably change until the mid-1970s for males, and, if anything, increased for females, indicating, that, in these countries, there was no earlier favourable modification in risk factor exposure. The recent falls, in contrast, were mainly on a period of death basis. This indicates that the main underlying determinant is related to therapeutic advancements.	Early RCTs comparing Cimetidine and placebo are difficult to interpret due to methodological inconsistencies and design problems. With the publication of the first USA RCT in 1978 reporting superiority for cimetidine for only 2 weeks of treatment, produced scepticism. A methodological review was conducted of the 16 RCTs published in English throughout 1980 testing cimetidine in endoscopically documented duodenal ulcer. The lack of a clinical classification of disease severity, the failure to consider the additional effect of iatrotherapy (the healing effect of the investigator), the failure to separate duodenitis from ulceration and to note transitions--change in duodenitis and change in ulcer size, and the failure to calculate beta error statistics for "negative" RCTs were methodological problems in explaining such disparate results[104].
Score		2	1
Commentary: The most recent **key intervention** seems to have been the introduction of H2 blockers in **1976**, although this was on top of earlier surgical advances. However RCTs of H2 blockers have used intermediate outcomes (such as ulcer healing) rather than mortality and the main source of evidence for population-level effectiveness is the observation of period effects in mortality data.			

Condition	Intervention(s)	How much of any decline can be attributed to health care? (What other factors may have been important?)	Evidence from patient-level studies of 30% or more decline in mortality linked to one or more interventions
Renal failure	Haemodialysis: **1944**, Netherlands (Kolf artificial kidney) Peritoneal dialysis Penicillin to treat streptococcal infection and thus prevent post-streptococcal glomeruloneprhritis **1940** Renal transplantation (First graft to function briefly in USA **1950** but soon rejected; first twin transplant **1954**; first unrelated successful transplants **1960**s). Unrelated transplants only possible once effective immunosupression available. Major advance was introduction of ciclosprin in **1980**s	A study conducted in New York, USA, concluded that over-all death rates from renal disease in the less than 25 age group declined from 4.6 per 100,000 in 1950 to 2.3 per 100,000 in 1970. This decrease in death was attributed to successful management of nephritis and nephrosis, A similar trend was found for the United States as a whole. The decline in deaths from nephritis and nephrosis could possibly be explained by a change in the natural history of these diseases. Between 1988 and 1996 half life of renal transplants not immediately rejected increased from 8.8 to 17.9 years. [105] 56% reduction in the risk of death within 1995-1999 cohorts of European studies (RR 0.44, 95% CI 0.39-0.50) compared to 1980-1984 cohort. [106] Age-specific death rates for nephritis and nephroses in England and Wales during 1949-65 have decreased. The death-rates for nephritis and nephrosis and infections of the kidney combined showed a decrease in men at all ages and in women below the age of 65 years. [107]	We could find no trials comparing dialysis or transplant with no treatment although the natural history of end stage renal disease is such that cases are uniformly fatal. Trials of ciclosporin invariably added it to existing immunosuppressant regimes based on prednisolone and azothiaprin. Ciclosporin A combined with prednisone was compared with standard immunosuppressive therapy (antilymphoblast globulin, prednisone, and azathioprine) in a prospective randomized trial of 100 mismatched, living related donor and cadaveric renal transplants. The results demonstrated ciclosporin A plus prednisone to be an effective immunosuppressive regimen for renal transplantation. The actuarial graft survival at 1 year was 93% for patients treated with ciclosporin A and 81% for patients treated with conventional immunosuppression. Patient survival was 98% for the ciclosporin A group and 100% for the conventional group. Ciclosporin A-treated patients had fewer rejection episodes and fewer infection, complications including a marked decrease in the incidence of posttransplant cytomegalovirus infection. The side effects of ciclosporin A were mild, but nephrotoxicity caused by ciclosporin A was frequent and significant. Nephrotoxicity was reversible and managed by decreasing the daily ciclosporin A dose. The trial concluded that the combination of ciclosporin A plus prednisone provided an alternative immunosuppressive regimen for renal transplants.[108]
Score		2	2
Commentary: The two **key interventions** are renal transplantation and dialysis, with improved outcomes reflecting expansion of treatment and greater experience in understanding the disease processes involved and in managing complications. The introduction of cyclosporine led to improvements in graft survival, but from an already quite high level.			

Condition	Intervention(s)	How much of any decline can be attributed to health care? (What other factors may have been important?)	Evidence from patient-level studies of 30% or more decline in mortality linked to one or more interventions
Congenital heart disease	Catheter Cardiopulmonary bypass : mid **1950**s. Deep hypothermia and circulatory arrest (DHCA): late **1960**s and early **1970**s	The term "Congenital heart disease" includes a wide spectrum of conditions from relatively minor atrial septal defects to major malformations incompatible with survival without immediate surgical intervention (such as transposition of the great vessels). Most of the research has looked at specific disorders and therefore it is difficult to ascertain the precise contribution of treatment to declines in mortality. Interventional cardiology offers patients minimally invasive alternatives to surgery. Device closures can now be treated with a standard transcatheter procedure using a closure device mounted on a balloon catheter. Cardiopulmonary bypass in mid 1950's. In late 1960s and early 1970s, the technique of deep hypothermia and circulatory arrest (DHCA) was developed in Japan and Sir Brian Barratt-Boyes in New Zealand used Kyoto technique (DHCA) to repair many infants and small children with complex congenital heart diseases (CHD). The introduction of DHCA was an important development in the history of the treatment of CHD, allowing the approach of previously unrepairable lesions. Open heart surgery in neonates has been adopted worldwide since Castaneda in Boston performed neonatal arterial switch in mid 1980s.	To determine long-term survival and the cause of death after repair of one of eight congenital heart defects in childhood. A cohort study conducted in Oregon, USA amongst children aged 18 years or younger with one of eight congenital heart defects was repaired surgically between 1958 and 1989. Follow-up of this cohort of 2701 individuals was obtained. Mortality from cardiac and noncardiac causes was recorded. Results showed that age at surgery and operative mortality decreased significantly over this 30 year period. Late cardiac mortality at 25 years after surgery was 5% for tetralogy of Fallot and isolated ventricular septal defect, 10% for coarctation of the aorta, 17% for aortic stenosis, 5% for pulmonary stenosis, and less than 1% for patent ductus arteriosus; there were no late cardiac deaths after atrial septal defect repair. For transposition, late cardiac mortality was 15% at 15 years after the Mustard operation and was 2% at 10 years after the Senning operation. Many of these abnormalities (exceptions being ventricular and atrial septal defects) were associated with a very high mortality prior to surgery, which seemed to indicate that advances in surgery have produced substantial reductions in mortality. Surgical repair of most congenital heart defects is associated with lingering cardiac mortality, particularly for aortic stenosis, coarctation, and transposition.[109]
Score		1	2
Commentary: Cardiac surgery remains the **key intervention**. However, it is difficult to identify a specific intervention given the diversity of disorders under this broad diagnostic category.			

Condition	Intervention(s)	How much of any decline can be attributed to health care? (What other factors may have been important?)	Evidence from patient-level studies of 30% or more decline in mortality linked to one or more interventions
Conditions originating in the perinatal period	Wallerstein exchange transfusion: **1945** (Wallerstein) perinatal mortality rate reduced in USA to 25%. [110] Antibiotics: **1940**s Prenatal diagnostics: *Amniocentesis* : **1953** (Douglas Bevis, 1953) Pathogenesis of Rh alloimmunisation: **1953** (Chown) [111] Anti-D immunoglobulin G (IgG) prophylaxis soon after delivery prevented sensitisation in Rh-negative women: **1960**s, UK/USA [112-114]. Special care baby units mid-**1960**s Intraperitoneal transfusion: 1963 and intravascular transfusion (IVT) **1981** reduced the perinatal morbidity and the mortality rate in developed countries was further reduced by 16%. [115;116] Perinatal medicine - local intensive and ventilator care **1981** Surfactant for infant respiratory distress syndrome approved by FDA in **1990**	Mortality rates: England: mortality rate fell from >30 in 1940 to 10 in 1975 linked to intoduction of free antenatal care, improved care during labour and antibiotic availablity (McFarlane et 1999 cited in Martines, 2005)[117]. Sweden: perinatal mortality declined at the end of the 19th century by 15-32% in those using midwives fro home deliveries (Hogberg, 2004 cited in Martines et al 2005)[117].	Experiments carried out in the USA, England and Canada showed that Rh immunisation was prevented by the administration of Rh antibody[112;113;118]. A Canadian trial over a two-year period (1966-1968) looked at the effectiveness of Rh Immune Globulin in the prevention of primary Rh immunisation amongst 1216 treated, and 500 non-treated childbearing women. Given in doses to unimmunised Rh negative women within three days of the birth of an ABO-compatible, Rh positive baby gives almost 100%protection against Rh immunisation by the pregnancy[119]
Score		2	1
Commentary: Perinatal deaths occur for a variety of reasons including prematurity and infection, and congenital abnormalities. The risk profile of live births has been changing for a variety of reasons, including increases in multiple births (due to IVF), reduction of congenital abnormalities (due to pre-natal diagnosis and termination), and changes in maternal age profiles. Hence, there is an irreducible minimum level, although this is difficult to ascertain as it will have changed over time. Comparisons across countries and over time are also complicated by definitional issues. There have been substantial declines in perinatal mortality rates (data from 1980-2000 only shown because of data availability). However, it is difficult to specify a **key intervention** because many of the specific innovations are indicated for only small proportions of births (rhesus immunisation, surfactant) and the overall improvements are like to have been due to the incremental introduction of a wide range of treatments, coupled with the accumulation of experience using them.			

Table 2.4 Conditions and key interventions included

ICD 9 code	Cause of death	Key intervention(s) that contributed to mortality decline	Starting time period of introduction	Availability of population level evidence	Availability of patient level evidence	Attributable to health care; total score	Effectiveness of interventions; total score
042-044	*HIV	Azidothymidine (AZT)	**Late 1980s**	✓	✓	**3**	**4**
153,154	Malignant colorectal neoplasm	A combination of specific treatments and improved management of the disease process i.e. screening	**1970s and early 1990s**	✓	✓	**3**	**1**
180	Malignant neoplasm of cervix uteri	Screening programme	**1970s**	✓	✓	**2**	**3**
186	*Malignant neoplasm of testes	Advances in surgery and adjuvant treatment i.e. cisplatin	**Late 1970s**	✓	✓	**3**	**2**
201	Hodgkin's disease	Combined chemotherapy	**1970s**	✓	✓	**3**	**4**
390-398	Rheumatic heart disease	Combined treatment; antibiotics and advanced surgical techniques i.e. Hufnagel and Harvey **(1953)** subsequently led to valve replacement by prosthesis (Starr and Edwards1961)	**1960s**	✓	✓	**1**	**2**
401-404	Hypertension	Antihypertensive drugs	**1960s**	✓	✓	**2**	**3**
410-414	Ischaemic heart disease	A combination of specific treatments and improved management of the disease process i.e. beta blockers	**1980s**	✓	✓	**2**	**4**
428-429	Heart failure	A combination of specific treatments and improved management of the disease process	**1980s**	✓	✓	**2**	**1**
430-438	Cerebrovascular disease	Treatment of hypertension	**1960s**	✓	†x	**3**	**1**
531, 532	Peptic ulcer	H2 blockers	**1970s**	✓	✓	**2**	**1**
584, 585, 586	Renal failure	Renal transplantation and dialysis	**1960s**	✓	✓	**2**	**2**
745-746	Congenital heart disease	Improved surgical technique e.g. Deep hypothermia and circulatory arrest (DHCA)	**1950s & 1960s**	✓	✓	**1**	**2**
760-779	*Conditions originating in the perinatal period	Incremental introduction of a wide range of treatments e.g. special care baby units	**1960s**	✓	✓	**2**	**1**

† Although clinical trials were not undertaken as such data has shown that treating hypertension prevents stroke and reduces fatality
*Exception to the rule; HIV was not classified under the 9th revision of ICD. Coding issue for neonatal deaths in the UK for the year 2000 and testicular cancer showed mortality rates remain high in other European Union countries

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3. Analysis of the introduction of new health care interventions (Results of work package 2)

Authors: Ragnar Westerling, Marcus Westin
Affiliation: Uppsala University, Sweden

3.1 Introduction

In work package 2 the introduction of new interventions that are likely to have reduced mortality from specific amenable causes of death is analyzed for seven European countries.
It does so by fulfilling the following tasks:

- To review the literature on the introduction of health care interventions
- To acquire data on diffusion of new interventions in selected countries
- To determine the timing of the introduction of interventions in these countries

3.1.1 The concept of Diffusion of Innovations

The concept Diffusion of Innovations (DOI) can arguably seem to emanate from the article by Ryan & Gross in 1943, in which they discussed the diffusion of usage of hybrid seed corn in two Iowa communities [1]. Perhaps most notable legacy of their work is the S-shaped curve (Fig 1) which illustrates the cumulative adoption of an innovation, validated by a multitude of subsequent studies. The theoretical framework with regard to DOI is closely associated with Everett Rogers ever since his book “Diffusion of innovation” [2]. Rogers defines DOI as “the process through which an innovation is communicated through certain channels over time among the members of a social system” [3].
There are five more or less distinctive key components in diffusion theory: the innovation, the adopter, the individual adoption process, the communication channel and the social system[3].

The Innovation
According to the theory of diffusion the individual perception of the innovation would influence the introduction of the innovation. There are several factors of importance for the perception of the innovation, for example, *Relative advantage* (does the individual perceive the change as beneficiary), *Compatibility* (innovation has to be in line with values, beliefs and needs of the individual), the *Complexity* of the innovation (simpler is “better”), *Trial ability* (is it possible to test the innovation before it needs to be fully implemented) and *Observability* (the ease with which potential adopters can observe early adopters).

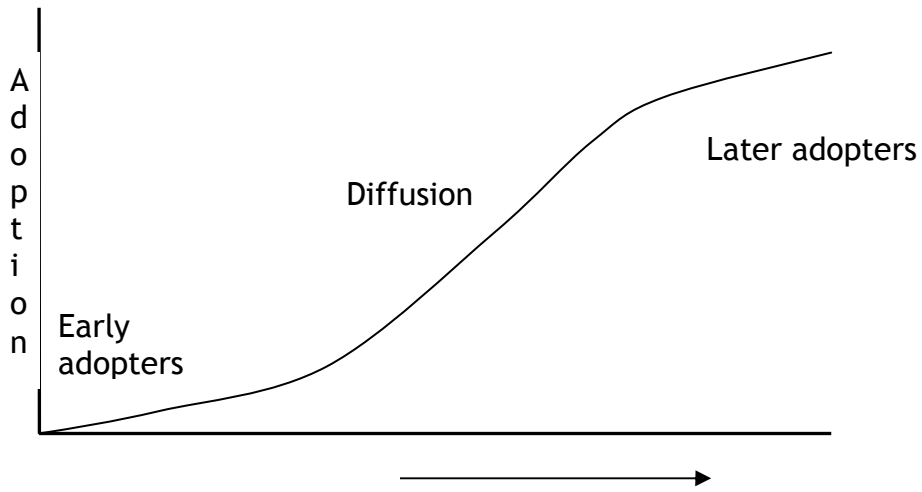

Figure 3.1. Cumulative adoption of an innovation

The Adopter

The adaptors can be characterized by their degree of innovativeness, classified into five different categories; Innovators, about 2,5 percent of the "population". They are not opinion leaders, but prone to novelty and with little to lose. Early adopters, constitutes the "population found between the 1st and 2nd SD and includes opinion leaders that interact with innovators and like-minded persons. They have the resources and risk tolerance to try new things. Thereafter follows the early majority, next third of the population, who tend to rely heavily on the early adopters. The Late majority, another third of the population, relies in turn on the early majority. They are considered more conservative and will not adopt an innovation until it is standard practice. Finally, the "laggards", (or traditionalists), caring for the 'old ways', are critical towards new ideas and will only accept it if the new idea has become mainstream or even tradition.

The Individual adoption process

The theories also include models for the individual adoption process, i.e. a stage-ordered model of awareness, persuasion, decision, implementation and continuation. These models describe the mental process through which an individual passes from first knowledge of an innovation to forming an attitude toward the innovation, to a decision to adopt or reject, to implementation of the new idea, and to confirmation of this decision.

Communication channels

A communication channel is the means by which messages get from one individual to another. Mass media channels are more effective in creating knowledge of innovations, whereas interpersonal channels are more effective in forming and changing attitudes toward a new idea, and thus in influencing the decision to adopt or reject a new idea. Most individuals evaluate an innovation, not on the basis of

scientific research by experts, but through the subjective evaluations of near-peers who have adopted the innovation.

The Social System

The social system constitutes a boundary within which an innovation diffuses. The structure of the social system; i.e. where diffusion trickles from informal opinion leaders to potential adopters by the perception of social pressure to adopt. These motivations and time of adoption are related to and can be predicted by each adopter's structural position in the network of relations that tie the social system together [4]

3.1.2 Previous empirical studies on diffusion of technology

There are also several published empirical studies on diffusion of innovation. Commonly, these are mainly descriptive studies showing the variation in the time of introduction of new innovations. Other studies aim at analyzing factors that could explain the process of diffusion. Furthermore, there has been concerns about inequity in medical care related to variations in the diffusion of innovation to different population groups such as racial and ethnic disparities [5-8] as well as gender and age differences [9]. Most studies are analyzing the diffusion inside a specific country but some make international comparisons [10-13]
.

Studies on diffusion of innovations have been based on a variety of empirical data such as health administrative data [7 14], medical records or questionnaires to or interviews with key informants [15-17]. For pharmaceutical drugs official data on registration as well as sales and prescribing statistics of pharmaceuticals [11 12 18] have been used. For advanced technical equipment international data are available which have been collected by OECD [19].

3.1.3 Controlling diffusion

Medical innovations are most likely to be, if adopted, a considerable driver of health care expenditures [20 21]. Even if there is an ongoing debate whether this increasing cost is balanced or even outweighed by total benefits [22], policy makers seek to seize control by not letting technical/medical innovations diffuse by chance. Health Technology Assessment (HTA) is thought to be a systematical process that will give policy makers sufficient information for deliberate decisions with regard to funding and investment. HTA also contain the systematic review of published research studies and scientific evidence that constitutes the backbone of Evidence Based Medicine (EBM)[23]. To what extent HTA has a substantial impact on diffusion is not particularly well investigated. One study shows that it at least influences diffusion, but not necessarily in the direction anticipated by the policy maker [24]. One specific outcome of HTA/EBM is clinical guidelines, which can be issued from health care connected governmental authorities in order to maximize cost-effectiveness, illustrated by the work done by NICE in GB and SBU in Sweden.

3.1.4 Implications on diffusion of innovations

Rogers's theoretical framework relies heavily upon the individual and decisions are made by individuals. However, since the introduction of EBM changes in clinical practice and clinicians behaviour are now increasingly linked also to organizational changes [25]. The implementation of clinical guidelines has gained much interest and today, the implementation rate (diffusion) of clinical guidelines in clinical practice can be understood by the theoretical framework developed initially by Rogers [26].
One major issue is the common finding that the transition of clinical research into daily clinical practice either fails or is delayed [27], which has shifted focus from adoption to implementation. This shift in focus is also valid when analyzing differences between new pharmaceuticals and cancer screening programs (or EBM/Clinical guidelines). This could be considered analogue to a shift from diffusion of innovations between peers in a horizontal network to a top-to-bottom implementation program instituted by "policy makers". The previous notion that diffusion of innovations is a linear process with focus on adopters has somewhat shifted into a much more contextual focus[28], where innovational practices and technologies are continuously interpreted and reframed in accordance with local context and priorities, including "negotiating" power balances between different professional groups [29 30].

3.2 Material and methods

A feasibility study concerning data on the timing of introduction of innovations was performed based on the key innovations for four potential indicators of amenable death in the project. These indicators were cervix cancer, breast cancer, testicular cancer and pneumonia. For each of these indicators the key innovation was defined according to the literature review results from the work of WP1. A questionnaire was developed and answered by the participating partners from the United Kingdom, the Netherlands, Germany, France, Spain, Estonia and Sweden. The partners were asked to identify sources of information about the introduction of the innovations and also describe the time of introduction. The source of data asked for were as follows: national decisions about organized medical programmes, national guidelines, committee reports, scientific papers, official registration of licensed pharmaceuticals and statistics of the sales/purchase of pharmaceuticals. The interventions included represented screening programmes for cervical cancer and breast cancer (mammography) and pharmaceutical treatment for breast cancer (Tamoxifen), testicular cancer (Cisplatin).

The feasibility study illustrated that it would be appropriate to use different sources of information in order to define the time for introduction of medical innovations. In some cases, there would be a time period during which the innovation is introduced in a specific country. Data would be available for the registration of pharmaceuticals and from most countries for the decision to introduce screening programmes. For pharmaceuticals, sales statistics would also be available in several countries but mainly these would not

be linked to the indication for prescription. For historical innovations the feasibility study showed that it would not be feasible to collect data on the timing of innovation. Based on the experiences of this first questionnaire another formula (Appendix A) was developed to collect the corresponding data for the defined amenable death indicators.

Innovations were included based on the information produced by WP1. For the list of preliminary indicators of amenable mortality, the defined key interventions which have been developed after 1970 were included in the study. Furthermore, a new generation of interventions introduced after 1970 with a potential effect on mortality was recognized from the work of WP1 and included in the study. The choice to include also these interventions is based on an assumption that not only one key intervention may be of importance for the outcome, but that for several conditions, there may be multiple interventions influencing the mortality trends. Historical innovations developed before 1970 were not included in the study.

A total of 18 innovations representing 14 causes of death were recognized and included in the final analyses. These interventions are listed in Table 3.1. The main part of these interventions involved causes of death related to malignant neoplasm and causes of death related to cardiovascular conditions. Both diagnostic and therapeutic measures as well as screening programs were included in the study. Several of the therapeutic interventions were pharmaceutical, mainly representing a single pharmaceutical with a key effect at the time of innovation. For some causes of death related to cancer the introduction of a pharmaceutical in combination with either of chemotherapy or high dose therapy was also studied. For cardiovascular diseases several of the interventions were preventive, but some were innovations that involved a more intensive acute treatment, for instance stroke and ischemic heart disease. Other interventions that included pharmaceuticals were related to HIV, peptic ulcer and immunosuppressive treatment for kidney transplantation.

Table 3.1. Interventions included in the analysis of timing of innovations

Cause of death	Intervention
HIV	➢ Treatment with anti-retroviral drugs azidothymidine and zidovudine
Malignant colorectal neoplasm	➢ Systematic diagnostic examination with colonoscopy/sigmoidoscopy
	➢ Treatment with Oxaliplatin
Malignant neoplasm of breast	➢ Mammography screening
	➢ Treatment with Tamoxifen
Malignant neoplasm of cervix	➢ Cervical screening
Malignant neoplasm of testes	➢ Treatment with Cisplatin
Hodgkin's disease	➢ High dose therapy, peripheral blood stem cell transplantation
Leukemia	➢ Improved treatment or management of the disease process and its complications for leukemia patients < 45 years
Rheumatic heart disease	➢ Arterial valve replacement
Hypertension	➢ Increase in numbers treated with antihypertensive drugs
Ischaemic heart disease	➢ Coronary care units for acute management Secondary prevention with beta blockers
Heart failure	➢ Treatment with ACE-inhibitors (such as Captopril or Enalapril)
Cerebrovascular disease	➢ Intensive management (CT scan;thrombolytic therapy; surgical treatment of aneurysms in subarachnoid haemorrhage) of acute stroke
	➢ Prevention by treatment of hypertension
Peptic ulcer	➢ Treatment with Cimetidine
Renal failure	➢ Immunosuppressive treatment with Cyklosporin for kidney transplantation and nephrosis

For these specific innovations, a questionnaire was developed and answered by the participating partners from the United Kingdom, the Netherlands, Germany, France, Spain, Estonia and Sweden. The partners collected data from official sources and from experts in the fields of medicine. In the questionnaire data were requested both at the start of the introduction of the innovation as well as the implementation. For the first part, documents on the official and organized introduction were asked for. These were for

instance, the registration year for pharmaceuticals and the year of national decisions, programs and guidelines for other interventions. To get information on the implementation of the interventions, data on scientific or committee reports evaluating the implementation were requested. For pharmaceuticals, sales statistics were collected, if available. This data may be used to verify that the medicine has been available in the respective country and also to analyze the speed of the implementation. To facilitate comparisons between countries, statistics on Daily Defined Doses (DDD) were asked for. Sales statistics were available from Sweden (1987-2008), Estonia (1999-2008), Germany (1999-2008; hospital data and privately insured not included) France (2002-2007), United Kingdom (mainly 1999; hospital data not included) and Spain (2000-2008; hospital data not included). The measure used differed between countries and pharmaceuticals. Sales statistics measured by DDD was mainly available from Sweden, Estonia and Germany.

Furthermore a literature review was performed for each innovation and country. Articles registered in MedLine with any of the key words (or words in title or abstract) “standards, guidelines, official policy, consensus development, evaluation studies or clinical trial” in combination with the terms for the innovation and the country names were scrutinized for applicable information. The country representatives were asked to comment on the data found and to collect further data based on the information.

The data from the questionnaire and literature review were combined in order to get several indicators of the diffusion process of the specific innovations in each country. We looked for both very early indicators of early adaptors introducing the method and indicators of a continued diffusion of the method.

To produce data for analyses of the association between timing of innovations and the mortality trend in WP5 a hypothesis of the expected time period for a favourable shift in mortality trend influenced by the introduction of the method was defined for the different innovations in each country. This hypothesis was based on the results from analyses of the combined data. The criteria for defining this year are presented in Table 3 (appendix A). A time period of 5-10 years was defined during which we would expect an effect on the mortality outcome (Table 3.3). The criteria for choosing this time period were based on theories on diffusion of innovation, scientific reviews of the implementation of innovations in general, specific information about the introduction and implementation in each country and estimates built on the data from all countries (Table 4-19, appendix A). For defining the last year of the time period, both an expected time period for the implementation and a time period for the potential medical effect on mortality were considered. However, the total time period studied was limited to a maximum of ten years in order to reduce the potential effects of other factors outside the control of this study on the mortality trends.

The starting year of the time period for the expected favourable shift in mortality was defined as the indicator year of the introduction of the innovation (Table 3, appendix A). For this indicator year a sensitivity analysis was performed indicating whether the year of introduction was classified based on a direct indication or not. The starting year of a clinical trial or study was considered to be a direct indication of the year of introduction (Table 3.2)

Table 3.2 The indicator year of the introduction of medical innovations expected to be followed by a favourable shift in mortality trend influenced by the innovation for selected causes of death.

	United Kingdom	***The Netherlands***	***Germany***	***France***	***Spain***	***Estonia***	***Sweden***
Treatment of HIV with the anti-retroviral drugs (Azidothymidine or Zidovudine)	1989*	1987*	1988*	1989*	1993*	1995	1988*
Systematic diagnostic examination of colorectal cancer with colonoscopy/sigmoidoscopy	1988*	1985*	1978*	1990	1987*	N.d	1981*
Treatment of colorectal cancer with Oxaliplatin	1995*	1999	2001	1988*	1994*	1999	1999
Screening for breast cancer with mammography	1979*	1975*	2001	1989	1992*	2005	1976*
Treatment of breast cancer with Tamoxifen	1976*	1981*	1981*	1981*	1988	1992	1976*
Screening for cervix cancer	1985	1980	1971	N.h.d.	N.h.d	2003	1970
Treatment of testicular cancer with Cisplatin	1976*	1976*	1973	1977*	1981	1995	1981*

	United Kingdom	***The Netherlands***	***Germany***	***France***	***Spain***	***Estonia***	***Sweden***
High dose therapy and peripheral blood stem cell transplantation for Hodgkin's disease	1999	1994*	1988	1992	1992	N.h.d.	1985
Improved treatment of disease process and complications for leukemia	1977*	1972*	1978*	1980*	1978*	N.d	1975*
Artificial valve replacement for rheumatic heart disease	N.h.d.	N.d.	N.d.	1970	1974*	1980	N.h.d
Increase in the number of patients treated for hypertension	1977	1979	1978	1975	1980	N.h.d.	1973
Coronary care units for acute management of myocardial infarction	N.h.d.	1977	N.d.	1995	1991	1980	1975
Medication for secondary prevention of myocardial infarction with beta-blockers.	1978*	1985	1979*	1987*	1982	1980	1976*
Treatment of heart failure with ACE-inhibitors[4]	1991*	1990*	1991*	1988	1991*	1994	1985*
Intensive management[1] of acute stroke	1998	1996	1996*	1992*	N.h. d.	1998	N.h.d.
Prevention of stroke by treatment of hypertension	1981*	1986*	1994	1993	1991	1997	1970*

Treatment of peptic ulcer with cimetidine	1981	1977	1979	1976*	1977	1993	1978
Immunosuppressive treatment with Cyklosporin for kidney transplantation of patients with acute nephritis and nephrosis	1980	1983*	1980	1982*	1985*	1993	1983*

3.3 Results

For about half of the innovations studied the timing of the introduction varied less than ten years between the different countries (Table 3.3). However, for other innovations the variation was larger.

In the field of prevention and treatment of circulatory diseases the introduction of most of the studied innovations varied between 6-10 years among the countries. For instance ACE inhibitors were introduced for heart failure in most countries in the late 1980s or early 1990s. However, these drugs were available for other indications earlier also in the countries where the registration for the specific indications studied were comparatively late.

Also for antihypertensive treatment the increase in the number of persons treated for hypertension mainly occurred in the same decade, i.e. in the 1970s. However, there was a difference between the countries when antihypertensive medication was used systematically for the prevention of stroke. In Sweden, prevention of cerebrovascular disease was introduced already in the 1970s, while in some other countries this was established first in the 1990s. For secondary prevention of myocardial infarction the introduction of beta-blockers was more equal in the different countries. This method was introduced in the late 1970s or 1980s.

For acute treatment of cardiovascular disease the results differed. Intensive management of cerebrovascular disease seems to have been introduced at a similar time in the different countries, i.e. in the 1990s.

Table 3.3 Expected time period for a favourable shift in mortality trend influenced by the introduction of medical innovations for selected causes of death

Innovation	*Country*						
	United Kingdom	***The Netherlands***	***Germany***	***France***	***Spain***	***Estonia***	***Sweden***
Treatment of HIV with the anti-retroviral drugs (Azidothymidine or Zidovudine)	1989-1996	1987-1994	1988-1995	1989-1996	1993-2000	1995-2004	1988-1996
Systematic diagnostic examination of colorectal cancer with colonoscopy/sigmoidoscopy	1988-1995	1985-1992	1978-1985	1990-1997	1987-1994	N.d	1981-1988
Treatment of colorectal cancer with Oxaliplatin	1995-2002	1999-2005	2001-2005	1988-1995	1994-2003	1999-2005	1999-2005
Screening for breast cancer with mammography	1979-1986	1975-1982	2001-2005	1989-1996	1992-1999	2005-	1976-1983
Treatment of breast cancer with Tamoxifen	1976-1983	1981-1988	1981-1988	1981-1988	1988-1995	1992-2001	1976-1985
Screening for cervix cancer	1985-1992	1980-1987	1971-1978	N.h.d.	N.h.d	2003-	1970-1977
Treatment of testicular cancer with Cisplatin	1976-1983	1976-1983	1973-1980	1977-1984	1981-1988	1995-2003	1981-1988
High dose therapy and peripheral blood stem cell transplantation for Hodgkin's disease	1999-	1994-2001	1988-1995	1992-1999	1992-1999	N.h.d.	1985-1992
Improved treatment of disease process and complications for leukemia	1977-1984	1972-1979	1978-1985	1980-1987	1978-1985	N.d	1975-1982
Artificial valve replacement for rheumatic heart disease	N.h.d.	N.d.	N.d.	1970-1977	1974-1981	1980-1987	N.h.d

Innovation	Country						
	United Kingdom	***The Netherlands***	***Germany***	***France***	***Spain***	***Estonia***	***Sweden***
Increase in the number of patients treated for hypertension	1977-1984	1979-1986	1978-1985	1975-1982	1980-1987	N.h.d.	1973-1980
Coronary care units for acute management of myocardial infarction	N.h.d.	1977-1984	N.d.	1995-2002	1991-1998	1980-1987	1975-1982
Medication for secondary prevention of myocardial infarction with beta-blockers.	1978-1985	1985-1992	1979-1986	1987-1994	1982-1989	1980-1987	1976-1983
Treatment of heart failure with ACE-inhibitors[4]	1991-1998	1990-1997	1991-1998	1988-1995	1991-1998	1994-2001	1985-1992
Intensive management[1] of acute stroke	1998-2005	1996--2003	1996-2003	1992-1999	N.h. d.	1998-2005	N.h.d.
Prevention of stroke by treatment of hypertension	1981-1990	1986-1995	1994-2003	1993-2002	1991-2000	1997-	1970-1979
Treatment of peptic ulcer with cimetidine	1981-1988	1977-1984	1979-1986	1976-1983	1977-1984	1993-2002	1978-1985
Immunosuppressive treatment with Cyklosporin for kidney transplantation of patients with acute nephritis and nephrosis	1980-1987	1983-1990	1980-1987	1982-1989	1985-1992	1993-2002	1983-1992

N.h.d.: No hypothesis defined;
N.d.: No data

1) CT scan;thrombolytic therapy(main basis for hypothesis); surgical treatment of aneurysms in subarachnoid haemorrhage

For coronary care units for acute management of ischaemic heart disease, the pattern seems to be more complex with a variation in introduction and a slow diffusion in some of the countries.

Also in the cancer field most of the innovations were introduced fairly close in time. In most cases the time span was between 7-9 years among the countries. This was for instance the case for both diagnostic procedures and treatment for colorectal cancer. Systematic diagnostic examination of malignant colorectal neoplasm with colonoscopy or sigmoidoscopy seems to mainly have been introduced in the 1980s, while treatment with Oxaliplatin was introduced in the 1990s or early 2000s. Also for leukaemia improved treatment of the disease process and complications seems to have been introduced fairly close in time, i.e. mainly in the 1970s. For high dose therapy and peripheral blood stem cell transplantation of patients with Hodgkin's disease the pattern was complex. There were indications of a variation in

introduction year and low numbers of patients treated during some periods as well as a professional debate about the method during the 1990s. Also, for cervical screening and mammography there was a considerable variation. In some countries organized cervical screening started in the 1970s or in the 1980s while in other countries this method has not yet been generally implemented. For mammography, the timing of introduction varied between the 1970s and the 2000s.

For some pharmaceuticals, the introduction was later in Estonia then in the other countries. In the cancer field, this was the case for treatment of testicular cancer with Cisplatin. This medication was introduced in most countries in the 1970s. In Estonia; however, the introduction seems to have been delayed until the 1990s. A similar pattern was found for treatment of peptic ulcer with Cimetidine. This was true also for treatment of breast cancer with Tamoxifen, although the variation was fairly large also among the other countries. Also for immunosuppressive treatment with Cyklosporin for kidney transplantation of patients with acute nephritis or nephrosis (renal failure) the introduction was later in Estonia, although the difference was not that large. The medication was introduced in most countries in the early 1980s but in Estonia first in the early 1990s. The introduction of treatment of HIV with anti-retroviral drugs, however, seems to have been fairly similar in the different countries in the late 1980s or early 1990s.

We used a wide range of data in order to indicate the introduction and diffusion of new innovations. In many cases the earliest indications found were reports form clinical trials or other clinical studies and in several cases these were published before the registration of medical drugs for specific indications. In other cases a national registration, decision or program was the starting point for the introduction, but these may also have been at place later on in the diffusion process. This was also the case for clinical guidelines, which in many cases was published after the first introduction of the method in a specific country.

The number of direct indications of the year of introduction varied between the different causes of deaths (Table 4). For treatment of HIV with anti-retroviral drugs, heart failure with ACE inhibitors, breast cancer with Tamoxifen and systematic diagnostic examination of colorectal cancer with colonoscopy or sigmoidscopy the indications of the year of introduction was mainly direct by for instance information on the starting year of a clinical trial. However, for coronary care units, increase in numbers treated for hypertension and cervical screening the information was more indirect.

3.4 Discussion

We found variation in diffusion of innovations in line with the theories of such diffusion. Differences between different countries are, with regard to diffusion theory, almost unconditional. One of the “pillar stones” in the concept of diffusion of innovations is the importance of the *social system*; i.e. the structural

system within a boundary wherein diffusion occurs, which may vary between countries [31]. The theory is as applicable for comparing the diffusion between different commodities within one system as comparing the diffusion of the same commodity between different social systems. Thus, difference in social systems implies differences in diffusion. International comparisons with regard to how medical interventions diffuse in different countries exist, but the findings are not entirely homogenous, except for some aspects; countries with an above average health spend have an increased diffusion [24 32 33] and countries with single state agencies in control of health care expenditures are more prone to have control of diffusion (i.e. slows diffusion down) than states with multiple insurance schemes (rapids diffusion)[24 34]. It may hence be possible, to compare different countries with regard to being early adopters, early majority etc in analogy with the theory of diffusion of innovations.

For several pharmaceuticals first introduced in the 1970s and 1980s the introduction period was fairly similar in most countries with the exception for Estonia, in which the introduction of for instance Cimetidine, Cisplatin and Cyklosporin seems to have been delayed until the 1990s. For the later developed drugs Oxaliplatin and anti-retroviral drugs, however the variation was much smaller. These results are consistent with the aspiration from the European countries to harmonize regulations with regards to medicines and other pharmaceutical products. The concept of the establishment of the Multi State Licensing Procedure in 1975 was that pharmaceuticals that had been approved in one member country should be authorized in other countries. This procedure, which was not that overly successful in the beginning, was replaced in 1987 by the Concertation Procedure, which in turn was replaced in 1995 by the foundation of EMEA[35].

Of the more recently introduced pharmaceuticals; Oxaliplatin was first approved in France in 1996, and approved throughout the EU through the Mutual Recognition Procedure in 1999, France being the Reference Member State. Zidovudine was first approved in 1987 through national licenses, before the Concertation Procedure became mandatory for HIV/AIDS products.

For cardiovascular diseases several drugs often have been available for other indications, mainly for hypertension, before they were introduced for treatment or prevention of the specific cardiovascular diseases such as heart failure (ACE-inhibitors), primary prevention of cerebrovascular disease (antihypertensive medications) and secondary prevention of ischaemic heart disease (Beta-blocker). However, the patient groups may somewhat overlap and the drugs may have had an impact on mortality trends for different cardiovascular diseases. The main effect one could expect would be that the favourable shift in mortality for heart failure, stroke and myocardial infarction may have occurred somewhat earlier since a number of patients at risk may have received the treatment earlier but for other indications, i.e. mainly for hypertension.

We used a wide range of data to analyse the diffusion of new innovations in the different countries. Different kind of data seems to have represented different phases of the implementation process. For

instance clinical trials often were the starting point of the process while clinical guidelines in many cases were published after the first introduction.

The implementation rate of clinical guidelines was investigated in a systematic review of the literature on the implementation of clinical guidelines; where argumentation about compliance rate applied Rogers's theoretical framework. Complexity and trialability of the clinical guidelines explained 47 % of the observed variability in compliance rates; if complexity was high then compliance was low and if trialability was judged by authors to be high then compliance was high. The compliance rate overall was a merely 54 %, over a nine-year period [38].

The timing of different guidelines varied between different countries. However, often the year of publication was close among most countries. Yet, in some cases a publication was earlier in one country, such as the national guidelines for prevention of cerebrovascular disease in Sweden. Moreover, reports state that the innovations had been in use in a specific country before the national publications supporting this use, e.g. coronary care units in Estonia. In Estonia, the practice of having treatment guidelines was not part of the medical culture during Soviet time and guidelines have therefore been published more recently[37] .

Greenhalgh summarizes, using the concept of diffusion of innovations as a model, reasons why there is such a resistance to adopt clinical guidelines [26]: 1) There is a lack of perceived relative advantage since new evidence from clinical trials are not apparent. 2) Interpretation of the evidence is difficult and complexity is high. 3) Guidelines may be perceived as incompatible with existing practice and values. 4) Trialability is low, since guidelines for single rather simple procedures may require extensive changes in how the workplace/organization is composed. 5) Perceived observability is low, for doctor and patient alike. 6) There is a limited space for re-invention or local adaptation. These are findings consistent with other systematic reviews [39].

The date when national decisions were made about screening programmes varied considerably. The time period for implementation also seems to be fairly long and different health administrative areas are reported to differ. Cancer screening programs are based on strong evidence for reducing morbidity and mortality [40] and mass screening programs have been advocated and recommended both in Europe and the US [41]. Some studies show that implementation rates are not in accordance with recommendations [42] [43], even though early screening tests are supposedly quickly adapted in medical social systems [44]. Reasons for this seem to be closely related to those that explain the slow adoption of clinical guidelines, i.e. relative advantages are not obvious: Screening programs may be costly and time-consuming. The degree of complexity may also be a hinder if procedures require high levels of expertise. Trialability may be low, since staffing pattern may not match intervention requirements [45]. There may also be a limited space for local adaptations.

There is also an equity-dilemma with regard to cancer screening tests that can be interpreted with the help of theories about the diffusion of innovations. Even though screening tests have been successful in improving cancer survival rates [42], certain groups in the population seem not to have been screened (they may be characterized as late adopters or laggards), not surprisingly the socio-economically most disadvantaged [43 46] . This variation in access to cancer screening tests is in line with theories on diffusion since Rogers has stated that the diffusion process may follow a socio-economic gradient [31].

However, even though diffusion theory has been successful with regard to understanding the adoption of innovations by individuals, it has been criticized for being less useful with regard to understanding diffusion among organizations; hence diffusion theory has somewhat evolved into an dissemination theory which is also applicable at the organizational level[47]. Diffusion may be defined as a passive process by which a program or product is absorbed into more widespread use, whereas top-to-bottom implementation of cancer screening programs and guidelines are said to be disseminated, defined as an active promotion or support of a programme to encourage its widespread adoption (which includes implementation) [45].

When analyzing differences in adoption/implementation, it might be appropriate to differentiate national screening programmes and clinical guidelines from pharmaceuticals. The rationale for doing this is that screening programmes strongly resemble clinical guidelines with regard to the diffusion process. Cancer screening programmes seem to suffer from the same limitations in adoption/implantation as clinical guidelines [45] and hence they differentiate from pharmaceuticals. Pharmaceuticals fit more easily into the classical diffusion theory, while the guidelines and screening programmes might benefit from being discussed in a more dissemination theory setting.

According to Rogers successful diffusion can be facilitated by how well the communication strategy is planned [31]. Crucial are not only the early adopters and innovators but also change agents and opinion leaders. The change agents may facilitate that innovators and early adopters can exchange crucial information. The opinion leaders may have a powerful impact on the social influences that are at the centre of interpersonal communication networks[29] [31]. There seems to be a difference between pharmaceuticals and cancer screening programs/guidelines with regard to the recruitment of change agents/opinion leaders. For pharmaceuticals, the promotion is mainly mastered by pharmaceutical companies. For cancer screening programmes and clinical guidelines, however, national organizations and authorities are responsible for the implementation and they may not yet have developed the same implementation skills.

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4. Building a harmonised data base (Results of work package 3)

Authors: Iris Plug, Rasmus Hoffmann, Johan Mackenbach
Affiliation: Erasmus MC, Rotterdam, The Netherlands

4.1 Introduction

The AMIEHS project is an international project in which 7 European countries collaborate to develop a new list of amenable mortality indicators. The innovative character of the selection process lies within the use of empirical analyses. To enable these analyses a harmonized database on trends in amenable mortality is necessary. This was constructed in work package 3. This database covers the time period between 1970 and 2005 in seven European countries.

4.2 Methods

4.2.1 Obtain data on AM mortality trends

All national statistical offices from the seven participating countries have been contacted and were sent an extensive description of the required database. Contact information is provided in Table 4.1. From all countries data on numbers of deaths were obtained for each year, by 5-year age group, sex and cause of death for the period between 1970 and 2005.

Table 4.1. Contact information AMIEHS database

Country	Statistical office	Contact
Estonia	Estonian causes of death registry	Mr G. Denissov Dr Mall Leinsalu
France	Inserm CepiDC	Dr G. Rey
Germany	Statistisches Bundesamt	Ms S. Schelo
Netherlands	Central Bureau of Statistics	Dr I.M. Deerenberg
Spain	National Spanish Statistics	Prof dr J.L. Alfonso
Sweden	National Board of Health and Welfare (Socialstyrelsen)	Ms C. Björkenstam
United Kingdom	Office for National Statistics (ONS)	Ms C. Wells

Database description

The observed period ranges from 1970 to 2005. If later calendar years were available these have been included. Data are depicted for both men and women separately. Numbers for the living population are the denominator of the death rates. Data on the deceased (the numerator of the death rates) exclude stillbirths.

For each combination of;

- year
- 5-year age group
- sex
- cause of death

data are given on

- number of person-years at risk during the observation period (midyear population)
- number of deaths due to the specific cause during the observation period

Causes of death

Information was gathered on all causes of death, ICD-8 (000-999) ICD-9 (1-999) and ICD10 (A00-Z99). Causes of death are classified in 3-digit coding. Corresponding ICD-9 and ICD-8 codes have been determined using ICD translation tables in collaboration with WP 4.

4.2.2 Evaluation of validity and completeness of data

Problems with estimation of rates are dealt with by checking the obtained data against time trends and international patterns of mortality rates published in official statistics. One of the databases available for a comparison with the obtained data is the Health for All databases from the WHO/Europe. To get insight into the validity of the data we are obtaining indicators on quality of cause-of-death certification in the different countries, e.g. the % of deaths with “unknown” or “not specified” codes. Problems with changes in the coding of causes of death have already been identified but will be addressed in detail in WP 4.

4.2.3 Preparation of a harmonized data base

All databases have been prepared in SPSS which is easy to be changed to .csv format and other statistical packages. All national databases have been harmonized into one database which contains one record for each combination of country, year, sex and age group. For each combination the number of deaths and the number of person years is provided according to cause of death. All participating countries have received the separate databases. A detailed description of the data sources, evaluations, and contents of the harmonised database is available.

4.3 Results

All seven separate databases have been made available to the participating partners. For both Spain and Germany mortality were available in a digital version starting from later years. Previous data had to be typed in by hand. In obtaining the data we have had to take into consideration some limitations. For Germany the availability of data differed between West (1970) and East Germany (1980). The constructed international database has enabled the work on WP4 and the analyses performed in WP5.

5.4 Discussion

An international harmonized mortality database has been constructed and made available to all participating partners in the AMIEHS project. The database has been the input for association analyses performed in work package 5. In these analyses ICD coding changes were taken into consideration through the application of correction factors developed in work package 4. Once the indicators have been identified an international database consisting of mortality data from over 30 European countries will be constructed through the same methodology used in the current work package in order to construct the electronic atlas in work package 7.

5. Analysis of the effect of changes in ICD coding (Results of work package 4)

Authors : Gregoire Rey, Eric Jougla
Affiliation : Institut national de la santé et de la recherche médicale – CépiDc, Paris, France

5.1 Introduction

The study of cause-specific mortality time series is one of the main sources of information for public health monitoring.[1-3] However, while demonstrative and striking use can be made of such trends when communicating with the general public, many concerns relating to the data production process have to be addressed. More specifically, it is necessary to evaluate, and, if necessary, correct artifacts due to data production changes that may bias the interpretation of time trends over a study period.

Mortality databases production process and related time series analysis issues

The production process of mortality databases is similar in many European countries (particularly in Western Europe) since the end of World War 2.

When a death occurs, a medical certificate, generally based on the international form recommended by WHO,[4] is filled in by a physician. This death certificate reports, in a first part, the different steps of the morbid process leading to death and, in a second part, other significant conditions that may have contributed to death.

The death certificate is then forwarded to a national (e.g. France) or regional (e.g. Germany) coding office, where it is coded using the International Classification of Diseases (ICD). The ICD was first published at the end of the 19th century[5]. It has been regularly reviewed and improved. The tenth revision (ICD10) is now used by most of the countries. Currently, the ICD10 includes approximately 12,000 categories. Since ICD6 (1948), the concept of the underlying cause is defined and rules and directives for the selection of the underlying cause have been precisely stated. This procedure is based on the international form of death certificate also introduced since ICD6. Although the underlying cause of death is generally accompanied by several other causes (associated, intermediate or terminal causes), it is the most commonly used in statistical analyses.

Generally, deaths are coded using the same ICD revision within each calendar year. The dates of the ICD revision used by each European country are well documented (Table 5.1).

Underlying cause coding is a complex process and thus implies potential between-coder coding differences. These differences may produce coding discrepancies over time and space. This is why, in addition to ICD revisions, coding may induce variations in the causes of death by period, region or country. This situation has resulted in countries using increasingly automated coding systems (ACS).

Table 5.1 - Dates of ICD change and implementation of Automatic Coding System (ACS) in European countries

COUNTRY	ICD8	ICD9	ICD10	ACS
Austria	1969	1980	2002	
Belgium	1968	1979	1998	
Croatia		1985	1995	
Czech Republic		1986	1994	
Denmark	1969		1994	2002
Estonia		1981	1997	2005
Finland	1969	1987	1996	
France	1968	1979	2000	2000
Germany	1968	1979	1998	2008
Greece	1968	1979		
Hungary	1969	1979	1996	2005
Iceland	1971	1981	1996	
Ireland	1968	1979	2007	2007
Italy	1968	1979	2003	1995
Lithuania		1981	1998	
Luxembourg	1971	1979	1998	
Malta	1968	1979	1995	
Netherlands	1969	1979	1996	
Norway	1969	1986	1996	2005
Poland	1969	1980	1997	
Portugal	1971	1980	2002	
Romania	1969	1980	1999	
Slovakia		1992	1994	
Slovenia		1985	1997	
Spain	1968	1980	1999	
Sweden	1969	1987	1997	1987
Switzerland	1969		1995	
United Kingdom	1968	1979	2001	1993

ACS: Automatic coding system

Historical analysis of mortality by cause on large periods may be biased by data in comparability over time. Indeed, as shown in the data production process description, variations in mortality trends may be attributable to:

- An evolution of the death certification, depending on:

- the state of medical knowledge,
- instructions given to fill in the certificate,
- the death certificate form used (WHO standard, number of lines, electronic certification…).

- An evolution of the coding process, depending on:

- a change in ICD revision used, implying a distribution of the deaths in different causes categories,
- non documented coding modifications (e.g. new instruction to coders in rules application),
- the use of an automatic coding system, which could induce the application of more strict and standardized rules and potentially modify the selection of the underlying cause.

- An actual historical variations of mortality by cause.

Methods to take into account coding variations in mortality by cause of death time series

The methods of analyzing actual historical variations in mortality by cause of death and taking into account data production process changes are essentially related to change in the coding process. Of these methods, three main kinds can be distinguished: bridge-coding, concordance table and cause recombination, and time series analysis-based methods.

Bridge coding

The bridge-coding method is used when there is a major change in the coding process (ICD version change or switch from a manual to an automatic coding system). The method consists in coding a large set of death certificates twice, applying the rules prevailing before and after the change. The ratios of numbers of death calculated by cause category before and after the change, called "comparability ratios", generate information for trend analyses and characterization of "jumps" in mortality time series. However, analyses of long-period time series do not necessarily use comparability ratios.[1, 6]

Bridge-coding analyses have been carried out in the USA and England and Wales for each ICD change since ICD8.[7-12] Bridge-coding analysis was also used and generated detailed results for the change from ICD9 to ICD10 in some countries (Scotland, Sweden, Italy, Spain, France and Canada).[13-18] However, to the authors' knowledge, most European countries have not implemented bridge coding to assess ICD changes. Comparability ratios are heterogeneous between country, most likely because of variations in intra-group composition of causes of death, reporting practices and ICD-

coding interpretation. Therefore, it is unlikely that a comparability ratio for one country can be inferred from the results of other countries.

Table 5.2 - Summary of the ratios obtained from the bridge coding between ICD9 and ICD10 performed in different countries

ICD10 Chapter	ICD10	ICD9	Title	CANADA	ENGLAND WALES	FRANCE	ITALY	SCOTLAND	SPAIN	SWEDEN	USA
I	A00-B99	001-139	Certain infectious and parasitic diseases	1.08	1.08	1.38	1.30	1.21	1.36	1.22	1.11
II	C00-D48	140-239	Neoplasms	1.01	1.03	1.01	1.01	1.02	1.01	1.02	1.01
III	D50-D89	280-289	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	0.91	0.58	0.86	0.86	0.63	0.67	0.49	0.96
IV	E00-E90	240-279	Endocrine, nutritional and metabolic diseases	1.04	1.04	1.13	1.06	1.05	0.86	0.96	1.02
V	F00-F99	290-319	Mental and behavioural disorders	0.84	1.21	1.09	0.80	1.23	NA	0.92	NA
VI	G00-G99	320-359	Diseases of the nervous system		1.50	1.25	1.15				
VII	H00-H59	360-379	Diseases of the eye and adnexa	1.33	1.00			1.43	1.33	1.20	1.35
VIII	H60-H95	380-389	Diseases of the ear and mastoid process		0.71						
IX	I00-I99	390-459	Diseases of the circulatory system	0.99	1.04	1.00	0.97	1.02	0.97	1.01	1.00
X	J00-J99	460-519	Diseases of the respiratory system	0.85	0.78	0.86	0.97	0.78	1.05	0.88	0.92
XI	K00-K93	520-579	Diseases of the digestive system	1.02	1.02	0.93	0.96	1.02	1.00	0.99	1.02
XII	L00-L99	680-709	Diseases of the skin and subcutaneous tissue	1.05	1.00	0.86	1.30	1.04	1.09	1.02	NA
XIII	M00-M99	710-739	Diseases of the musculoskeletal system and connective tissue	1.36	1.39	1.09	1.37	1.35	1.07	1.15	NA
XIV	N00-N99	580-629	Diseases of the genitourinary system	1.01	1.00	0.94	1.08	1.03	1.00	0.98	1.22
XV	O00-O99	630-676	Pregnancy, childbirth and the puerperium	NA	1.10	1.50	NA	1.14	1.00	2.00	NA
XVI	P00-P96	760-779	Certain conditions originating in the perinatal period	1.03	1.20	1.03	NA	0.94	1.06	1.02	1.07
XVII	Q00-Q99	740-759	Congenital malformations, deformations and chromosomal abnormalities	0.91	1.13	1.08	NA	1.04	1.00	1.05	0.85
XVIII	R00-R99	780-799	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	1.00	1.00	0.93	1.47	1.03	1.14	1.02	0.96
XX	V01-Y89	E800-E999	External causes of morbidity and mortality	1.02	1.00	0.96	0.94	1.01	1.00	1.04	1.01

Concordance table and cause recombination

The concordance table and cause recombination approach consists in determining the most consistent cause categories, under medical consideration, for two successive ICD revisions. Analysis of the mortality using the resulting categories is then theoretically little influenced by coding changes. This approach typically only works well when considering the coding of any particular cause reported on the death certificate. It is often not effective when considering changes in the rules for selecting the underlying cause of death, especially when such rule changes favour the selection of one cause over another. It is often impossible to recombine codes to fully account for these changes.

The method was used on French, Dutch and Swedish data.[19-21] This approach, complex and time consuming when it is applied to a single country, is even more difficult to use in the context of an international study.[22]

Time series analysis

The time series analysis method consists in looking for sustainable jumps, evaluating their statistical significance and amplitude, and possibly smoothing the time series by adjusting the data with correction factors. The method is easy to document, even when the volume of data considered is large (many countries, many causes of death, etc.). Furthermore, the method is necessary when the time of the change in the data production process is unknown.[23] To the authors' knowledge, the detection of jumps in mortality data has rarely been undertaken,[22, 24] but, in particular for Janssen et al's work,[22] has given raise to fruitful international public health studies.[25-28]

However, the methods used in these studies did not take advantage of the recent development of automated jump detection methods in indexed data analysis (by time or other variables).[29-31] The interest of the automatic jump detection method resides in its ability to avoid the subjectivity of visual detection or a priori selection of jump positions.

This work package proposes a complement to a time series analysis method that was previously developed by Janssen et al.,[22] permitting to detect sustainable jumps attributable to changes in data production and to develop correction factors by age and gender in order to enable subsequent epidemiological analyses. The method is then applied to the different mortality time series considered in the AMIEHS project.

5.2 Method

General approach

The following step-by-step approach was adopted:

1. Given a list of selected causes of death, the ICD codes to be considered were determined by nosologists, based on the correspondence table method, while maintaining the medical consistency of the list of codes for the various ICD revisions.
2. An automated jump detection method was applied to the mortality rate time series for each of the selected causes of death.
3. For documented jumps (e.g. ICD changes), the available comparability ratios were compared to the amplitude of the estimated jumps. For non-documented jumps, general information feedback was requested from the national data producers.
4. For documented or plausible jump positions, the statistical significance of the between-age and -gender jump amplitude heterogeneity was evaluated by means of a regression model, and correction factors were deduced from the results.

Codes allocation

For 16 causes of death selected in the AMIEHS project, the method of allocating the ICD8, ICD9 and ICD10 codes was as follows:

- when the cause was included in the Eurostat 65 causes shortlist,[32] the codes defined by Eurostat were retained
- for other causes, two nosologists independently selected the optimal 3-digit codes. Then, a final choice was made in order to minimize the coding-related jumps in cause-of-death specific time series analysis. Table 5.3 shows the related codes.

Table 5.3 - ICD8, ICD9 and ICD10 codes for the 16 selected causes of death

Cause name	ICD8	ICD9	ICD10
Cerebrovascular disease	430-438	430-438	I60-I69
Conditions originating in the perinatal period	760-779	760-779	P00-P96
Congenital heart disease	746	745-746	Q20-Q24
Heart failure	428-429	428-429	I50-I51
HIV	na	042-044	B20-B24
Hodgkin's disease	201	201	C81
Hypertension	400-404	401-404	I10-I13
Ischaemic heart disease	410-414	410-414	I20-I25
Leukaemia	204-207	204-208	C91-C95
Malignant colorectal neoplasm	153-154	153-154	C18-C21
Malignant neoplasm of breast	174	174	C50
Malignant neoplasm of cervix uteri	180	180	C53
Malignant neoplasm of testes	186	186	C62
Peptic ulcer	531, 532	531, 532	K25-K26
Renal failure	593, 792	584-586	N17-N19
Rheumatic heart disease	390-398	390-398	I00-I09

A specific issue concerned the Estonian data, which were provided under a Soviet shortlist format for years 1970 to 1993. The choice of the minimal category including the ICD codes was decided to build the corresponding Soviet codes. After further investigations, it appears that the following conditions were not enough specifically identified with Soviet codes to be analysed: Hodgkin's disease, heart failure, renal failure and conditions originating in the perinatal period.

The automatic jump detection method

Given that mortality analyses are often based on multiplicative assumptions, log-linear generalized models were used. Thus, the time series jump detection method was applied to the log mortality rates.

Let O_t, be the number of deaths during year t, p_t be the number of person-years and $L_t = \log\left(\frac{O_t}{p_t}\right)$ be the log mortality rate time series. The occurrence of jumps in the log mortality rate time series may be expressed as follows:

$$\log(E(O_t)) = \log(p_t) + g(t) + \sum_{t' \in S} d_{t'} \cdot 1_{(t>t')} ,$$

In which 'g' is a continuous function, S is the set of jump locations and $\{d_t, t \in S\}$ are the corresponding jump magnitudes.

In this model, g, S and $\{d_t, t \in S\}$ are all assumed unknown.

The method consists in three main steps:

1. A left and right limit of $E(L_t)$ were estimated, for each point t, using two local polynomial smoothers, denoted $P_l(t)$ and $P_r(t)$, fitted on [t - h, t) and (t, t + h], respectively, where h is the bandwidth for the estimation, to be estimated in further steps. If $t \notin S$, and the jumps location are distant from at least h, then, given that g is continuous, we expect $E(P_l(t)) = E(P_r(t)) = g(t)$. Else, if $t \in S$, we expect $E(P_l(t)) = g(t)$ and $E(P_r(t)) = g(t) + d_t$.

The noise σ of the L_t process is estimated as:

$$\hat{\sigma} = \frac{1}{T-1} \cdot \sum_t \min\left((L_t - P_l(t))^2, (L_t - P_r(t))^2\right)$$

The polynomial kernel of the smoothers could, a priori, be constant, linear or quadratic, depending on the number of observations and the curvature level of the time series. Since, in the present case, the number of observations was not greater than 40, and the time series was expected to be quite stable, a linear kernel was selected.

2. Considering $M(t) = P_r(t) - P_l(t)$, jump points were defined as points where the signal-to-noise ratio $\frac{|M(t)|}{\hat{\sigma}}$ was higher than a threshold C_α.

C_α was chosen such that, if 't' is not a jump point, $P\left(\frac{|M(t)|}{\hat{\sigma}} > C_\alpha\right) \leq \alpha$. The analytic calculation of C_α is given elsewhere [33]. In the following steps, α was set to 10^{-5} a low value, in order to avoid as much as possible false positive jumps.

Then, $S = \left\{t : \frac{|M(t)|}{\hat{\sigma}} > C_\alpha\right\}$ and $\left\{\hat{d}_t = M(t), t \in \hat{S}\right\}$ were directly estimated. When several jumps were detected in a time range less than the bandwidth, only the jump that maximized M(t) was retained.

3. The bandwidth h was estimated by minimizing the Hausdorff distance, [29] defined as:

$d_H(S,\hat{S};h) = \max\left\{\sup_{t_1\in\hat{S}} \inf_{t_2\in\hat{S}} |t_1 - t_2|, \inf_{t_1\in\hat{S}} \sup_{t_2\in\hat{S}} |t_1 - t_2|\right\}$, in which $d_H(S,\hat{S};h)$ was calculated through a bootstrap procedure, taking B, the number of batches used, equal to 1000. A full description of this method is given elsewhere.[33]

Age- and gender-heterogeneity test

Age categories were defined as the tertile of the cause-specific death counts.

Generally, when considering J different population groups (age and gender), a generalized additive model (GAM) with an over dispersed Poisson distribution is used.[34, 35] The model has the following form:

$$\log(E(O_{t,j})) = \log(p_{t,j}) + g_j(t) + \sum_{t'\in S} d_{t',j} \cdot 1_{(t>t')} ,$$

In which j is one of the J groups, 'g_j' are continuous functions fitted by a thin plate penalized regression spline, S is the set of jump locations and $\{d_{t,j}, t \in S\}$ are the corresponding jump magnitudes for group j.

S is supposed known, and the aim is to test, for each $t \in S$:

$$H0: d_{t,1} = \ldots = d_{t,J}$$

Backward variable selection was used to suppress, successively, age and gender from the model if their respective effects on the jump amplitude were not statistically significant, at the 5% level, using Wald's test.

The mgcv R package was used for this purpose.[36]

Correction factors

Correction factors were calculated for all confirmed jumps.

The correction factors were calculated for use in subsequent analyses, with a log-linear model of general form:

$$\log(E(O_t)) = \log(p_t) + c_t + f(X_t),$$

in which 't' is the year, between T_1 and T_2 (respectively equal to 1970 and 2006 in this study); c_t is the correction factor and $f(X_t)$ could be any function of independent variables, to be estimated.

The correction factors were set so that the last values of the corrected mortality rates were equal to the exact mortality rates, i.e. $c_{T_2} = 0$. This choice was based on the supposed superior quality and between-country comparability of the most recent year's data.

The foregoing results in the following definition of the correction factors c_t:

For $t \in [T_1, T_2]$,

$$c_t = \sum_{t' \in S, t' < t} d_{t'} - \sum_{t' \in S} d_{t'} = - \sum_{t' \in S, t' \geq t} d_{t'} .$$

The estimate of c_t was then directly obtained from the estimates of S and d_t detailed earlier.

A corrected version of the log mortality rate was then obtained as:

$$L_t^{cor} = L_t - c_t$$

Data producers of each country

The data producer's contacts were the following:

- Netherlands: Jan Kardaun, National Bureau of Statistics
- Spain: Maria Del Rosario Gonzales Garcia, National Statistics Institute
- Germany: Torsten Schelhase, Federal Statistical Office
- Sweden: Lar Age Johansson, National Board of Health and Welfare
- France: Gérard Pavillon, National Medical Research Institute
- UK: Cleone Rooney, Office for National Statistics
- Estonia: Gleb Denissov, Statistics Estonia

Questions asked to data producers

The list of jumps was sent to the data producers of all-countries. For each jump, the following questions were asked:

- Is the jump due to a coding change (Y/N)?
- What is the type of this coding change (ICD, Manual/Automated, National guidelines, other)?
- Does this change mainly explain the amplitude of the jump (Y/N)?
- Please give additional information (reference, internal observations, comments, other)

5.3 Results

Jump detection

By applying the jump detection method to all the time series, a set of 49 jumps was obtained (Table 5.4). Most of the jumps detected were concomitant with a known coding change (ICD updates or change from a manual to an automatic coding system). Some of the jumps (e.g. for heart failure and rheumatic heart disease) were of great amplitude and almost systematically observed in each country. For the former East Germany, most of the changes were concomitant with the reunification of Germany.

The answers from data producers, contacted to determine whether the jump was related to a data production issue, were consistent between countries. Most (excluding the "No answer", 42 out of 44) of the detected jumps were confirmed to be related to a coding change. The 3-digit coding constraint was given as an explanation for some jumps (rheumatic heart disease in France, ischaemic heart disease in Spain, etc.), specially when countries chose specific codes (Spain for malignant colorectal neoplasm). The 1990 and 1991 jumps in East Germany were related to a complete change of coding staff. However, most of the coding changes are not documented by a literature reference. No jump was detected for Estonia, which was mainly the result of very large variability of the time series considered.

Given the large proportion of confirmed jumps, we decided to exclude from subsequent treatment the jumps for which we received a negative answer from data producers.

Table 5.4 – Jumps in the log mortality rate time series for the 16 selected causes of death from 1970 to 2005 identified by the Polydect method

Country	Underlying cause of death	Year of the jump	Multiplicative factor[1]	Data producer confirmation	Proposed jump cause[2]
England and Wales	Cerebrovascular disease	2001	1.24	Yes	ICD10
	Conditions originating in the perinatal period	1986	0.09	No answer	No
	Conditions originating in the perinatal period	2001	2.78	Yes	ACS
	Heart failure	1979	3.59	Yes	ICD9
	Heart failure	1984	0.74	Yes	No
	Heart failure	1993	1.61	Yes	ACS
	Renal failure	1979	2.90	Yes	ICD9
	Renal failure	1993	2.33	Yes	ACS
	Rheumatic heart disease	1979	0.63	Yes	ICD9
	Rheumatic heart disease	2001	0.77	Yes	ICD10
France	Heart failure	1979	1.99	Yes	ICD9
	Hypertension	1979	0.71	Yes	ICD9
	Hypertension	1998	1.26	Yes	Death Certificate
	Malignant colorectal neoplasm	1979	0.92	Yes	ICD9
	Malignant colorectal neoplasm	2000	0.94	No	ICD10
	Peptic ulcer	1979	0.74	Yes	ICD9
	Peptic ulcer	2000	0.63	Yes	ICD10
	Rheumatic heart disease	1979	0.36	Yes	ICD9
	Rheumatic heart disease	2000	1.54	Yes	ICD10
East Germany	Cerebrovascular disease	1991	1.45	Yes	Reunion
	Conditions originating in the perinatal period	1991	0.46	Yes	Reunion
	Heart failure	1990	1.85	Yes	Reunion
	Heart failure	1991	0.52	Yes	Reunion
	Hypertension	1991	0.51	Yes	Reunion
	Ischaemic heart disease	1991	1.43	Yes	Reunion
	Malignant colorectal neoplasm	1991	1.21	Yes	Reunion
	Rheumatic heart disease	1998	1.14	Yes	ICD10
West Germany	Heart failure	1979	1.65	Yes	ICD9
	Hodgkin's disease	1994	0.59	No	No
	Ischaemic heart disease	1979	0.87	Yes	ICD9
	Rheumatic heart disease	1979	0.51	Yes	ICD9
Netherlands	Heart failure	1979	1.54	Yes	ICD9
	Heart failure	1996	0.76	No answer	ICD10
	Hypertension	1980	0.65	Yes	No
	Renal failure	1979	0.75	No answer	ICD9
	Rheumatic heart disease	1992	5.40	No answer	No
	Rheumatic heart disease	1996	0.13	No answer	ICD10
Spain	Conditions originating in the perinatal period	1975	2.94	Yes	Definition change
	Heart failure	1980	1.41	Yes	ICD9
	Ischaemic heart disease	1980	0.93	Yes	ICD9
	Malignant colorectal neoplasm	1980	0.78	Yes	ICD9
	Renal failure	1980	1.73	Yes	ICD9
Sweden	Heart failure	1987	5.55	Yes	ICD9
	Malignant neoplasm of testes	1974	1.33	Yes	No
	Malignant neoplasm of testes	1979	0.74	Yes	No
	Renal failure	1987	0.69	Yes	ICD9
	Renal failure	1997	1.23	Yes	ICD10
	Rheumatic heart disease	1982	0.08	Yes	Coding change
	Rheumatic heart disease	1987	15.33	Yes	ICD9

[1]: multiplicative factor of the mortality rate between the period before and after the detected jump
[2]: new coding, implementation of which may have caused the jump

It was possible to compare a few of the multiplicative factors with the comparative ratios generated by bridge-coding studies corresponding to ICD9 to ICD10 changes (Table 5.5). Especially, the large multiplicative factors (e.g. for rheumatic heart disease) had no related comparative ratios. Some coding changes were not detected by the jump detection method (Hodgkin's disease in England & Wales and Sweden, and renal failure in England & Wales). However, none of the detected jumps were found unrelated to a coding change.

Table 5.5 – Comparative ratios (CR) obtained from bridge coding and multiplicative factors (MF) estimated by the jump detection method - ICD9 to ICD10 coding change

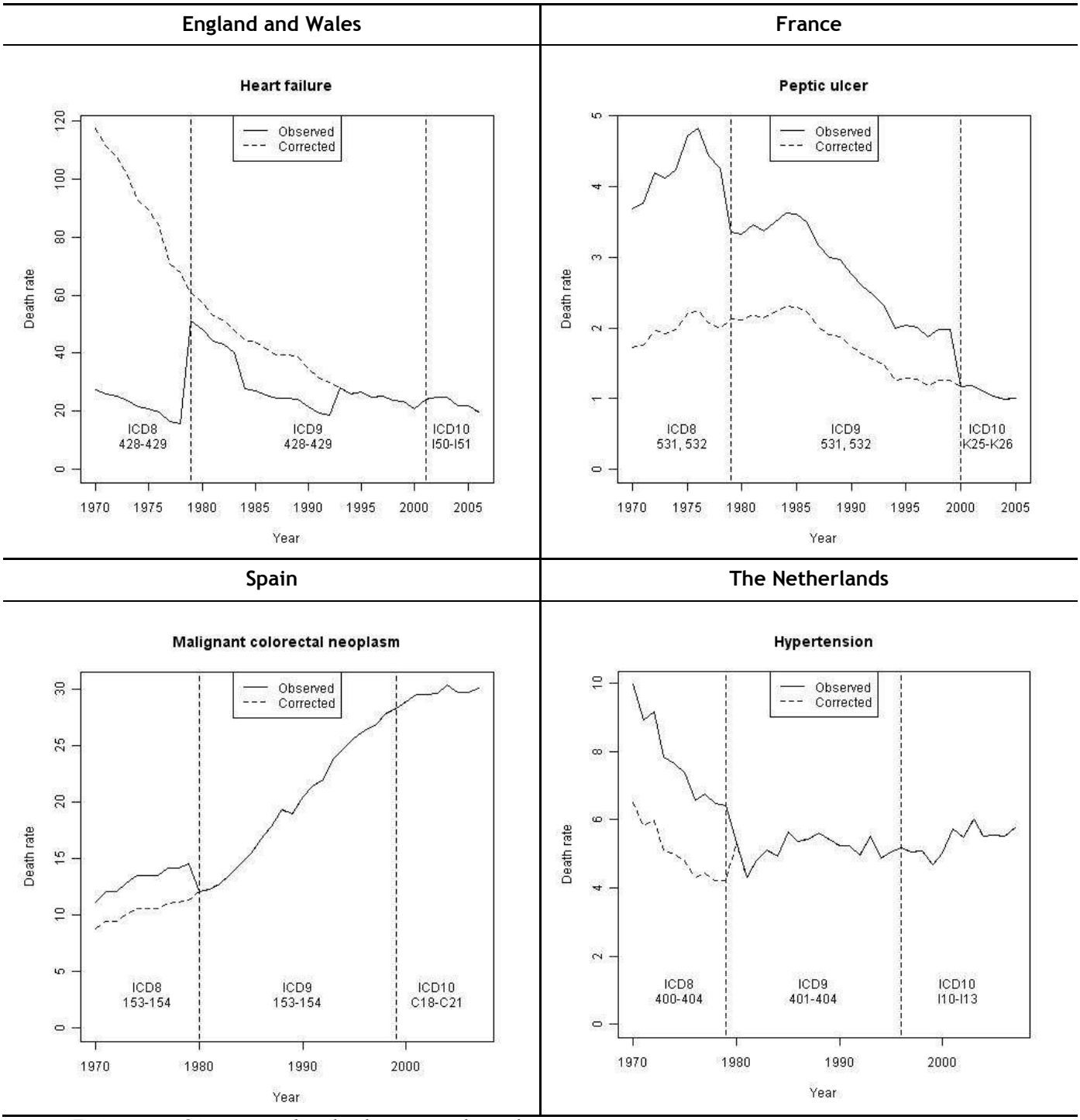
	France		England & Wales		Sweden		Spain	
Underlying cause of death	**CR**	**MF**	**CR**	**MF**	**CR**	**MF**	**CR**	**MF**
Cerebrovascular disease	0.97	1.00	1.13	1.13	1.03	1.00	-	1.00
Conditions originating in the perinatal period	1.03	1.00	-	2.24	1.02	1.00	-	1.00
Congenital heart disease	-	1.00	-	1.00	-	1.00	-	1.00
Heart failure	-	1.00	-	1.00	-	1.00	-	1.00
Hodgkin's disease		1.00	1.06	1.00	1.13	1.00	-	1.00
Hypertension	-	1.00	-	1.00	-	1.00	-	1.00
Ischaemic heart disease	1.03	1.00	1.01	1.00	1.00	1.00	1.00	1.00
Malignant colorectal neoplasm	0.97	0.94	1.01	1.00	0.99	1.00	1.00	1.00
Malignant neoplasm of cervix uteri	0.92	1.00	1.00	1.00	1.00	1.00	-	1.00
Malignant neoplasm of testes	-	1.00	0.99	1.00	-	1.00	-	1.00
Peptic ulcer	-	0.63	1.00	1.00	-	1.00	-	1.00
Renal failure	-	1.00	1.08	1.00	-	1.23	-	1.00
Rheumatic heart disease	-	1.54	-	0.77	-	1.00	-	1.00

CR: Comparative ratios obtained from bridge coding, calculated as the ratios of numbers of death calculated by cause category before and after the ICD change
MF: multiplicative factor of the mortality rate between the period before and after the ICD change, equal 1.00 when no jump was detected
- : Comparative ratio not available

Corrected mortality rate time series

Considering some of the most clear-cut time series, the profile of the corrected time series is quite different from that of the uncorrected series (Figure 5.1). It is noteworthy that the corrected curves do not reduced the general trends at the jump positions, which would have been the case if constant rather than linear kernel smoother was chosen. They rather prolong the trends, even if the jump is in the opposite direction to the general trend.

Figure 5.1: Examples of corrected mortality rate (per 100,000 people) time series



Estimates of jump amplitudes by age and gender

With regard to the jump amplitude heterogeneity test by age and gender, only 19 out of 47 jumps were not statistically significantly heterogeneous (Table 5.6a-b). Five of the jumps were heterogeneous by gender, 15 by age and 8 simultaneously by age and gender. While the jump amplitudes are of the same order by gender, even when statistically heterogeneous, they are of different orders when considered by age group. This was particularly marked for rheumatic heart disease and heart failure.

Table 5.6a – Multiplicative factor by age and gender, if statistically heterogeneous, for each detected jump

Country	Underlying cause of death	Year	Gender[2]	Multiplicative factor[1]		
				Age tertile[3]		
				1st	2nd	3rd
England and Wales	Cerebrovascular disease	2001	Both		1.13	
	Conditions originating in the perinatal period	1986	Both		0.10	
		2001	Both		2.24	
	Heart failure	1979	Male	4.78	3.86	3.34
			Female	4.22	3.41	2.95
		1984	Both	0.60	0.72	0.77
		1993	Both	1.83	1.58	1.37
	Renal failure	1979	Both		2.59	
		1993	Both	2.93	1.53	1.50
	Rheumatic heart disease	1979	Male	0.54	0.50	0.39
			Female	0.82	0.75	0.59
		2001	Both	0.87	0.94	0.75
France	Heart failure	1979	Both		1.91	
	Hypertension	1979	Male		0.63	
			Female		0.70	
		1998	Both	1.14	1.10	1.25
	Malignant colorectal neoplasm	1979	Both		0.91	
	Peptic ulcer	1979	Both		0.75	
		2000	Both		0.61	
	Rheumatic heart disease	1979	Male	0.39	0.32	0.22
			Female	0.62	0.51	0.35
		2000	Both		1.53	
East Germany	Cerebrovascular disease	1991	Both		1.40	
	Conditions originating in the perinatal period	1991	Both		0.52	
	Heart failure	1990	Both	1.71	1.46	1.27
		1991	Both		0.72	
	Hypertension	1991	Male	0.45	0.51	0.58
			Female	0.52	0.58	0.67
	Ischaemic heart disease	1991	Male	1.14	1.21	1.30
			Female	1.22	1.30	1.40
	Malignant colorectal neoplasm	1991	Male	1.14	1.17	1.32
			Female	1.04	1.07	1.20
	Rheumatic heart disease	1998	Male		0.92	
			Female		1.25	
West Germany	Heart failure	1979	Both		1.60	
	Ischaemic heart disease	1979	Male	0.98	0.92	0.76
			Female	0.93	0.88	0.72
	Rheumatic heart disease	1979	Male		0.46	
			Female		0.69	

[1]: multiplicative factor of the mortality rate between the period before and after the detected jump
[2,3]: multiplicative factor estimated by age and gender, if statistically heterogeneous at the 5% level. Age and gender categorical variables were selected with a backward procedure.
[3]: Age categories were defined by country and cause of death in order to include a third of the number of deaths

Table 5.6b – Multiplicative factor by age and gender, if statistically heterogeneous, for each detected jump

Country	Cause	Year	Gender[2]	Multiplicative factor[1]		
				Age tertile[3]		
				1st	2nd	3rd
Netherlands	Heart failure	1979	Male	2.15	1.33	1.23
			Female	1.86	1.15	1.06
		1996	Both	0.64	0.77	0.82
	Hypertension	1980	Both	0.95	0.81	0.70
	Renal failure	1979	Both	0.41	0.72	0.63
	Rheumatic heart disease	1992	Both	0.89	2.76	5.32
		1996	Both		0.42	
Spain	Conditions originating in the perinatal period	1975	Male		2.85	
			Female		3.08	
	Heart failure	1980	Both		1.46	
	Ischaemic heart disease	1980	Both		0.94	
	Malignant colorectal neoplasm	1980	Male		0.84	
			Female		0.75	
	Renal failure	1980	Both	1.66	1.57	1.24
Sweden	Heart failure	1987	Both	3.57	7.55	7.99
	Malignant neoplasm of testes	1974	Both		1.40	
		1979	Both	0.41	0.72	0.88
	Renal failure	1987	Both		0.65	
		1997	Both	1.59	0.88	1.23
	Rheumatic heart disease	1982	Both		0.12	
		1987	Both	5.71	7.20	14.27

[1]: multiplicative factor of the mortality rate between the period before and after the detected jump
[2,3]: multiplicative factor estimated by age and gender, if statistically heterogeneous at the 5% level. Age and gender categorical variables were selected with a backward procedure.
[3]: Age categories were defined by country and cause of death in order to include a third of the number of deaths

5.4 Discussion

The originality of the methodology reported herein mainly resides in its ability to detect jumps automatically using the Polydect method, without a priori or visual investigation for jump positions. In addition, application of the method to a large dataset is less time consuming and less human-dependent than any other known method.

Some methodological choices were made, such as the choice of a linear kernel smoother and the choice of the probability α of detecting fake jumps. Considering a constant kernel, smoother or different values of α slightly affected the final set of detected jumps, and only for time series in which the jump amplitudes were of an order comparable to that of the overall noise of the time series. Choosing a low value of α insured a better accuracy in the jump's amplitude estimation, which is more statistically stable when the jump is of far larger amplitude than the overall noise of the time series. According to the visual inspection of time series graphs and comparable bridge coding results, jump's amplitude estimates were reliable enough to be used in subsequent analyses.

The codes used in this study to characterize the conditions were not chosen to be used in all contexts. Indeed, they were allocated with the constraint of being comparable between three ICDs and based on 3-digit codes. Taking each ICD individually would certainly have led to select other codes.

The method is designed to detect sustained jumps. Therefore, it is not sensitive to the occurrence of one-year outliers in time-series data and it does not necessitate considering them separately, unlike other methods.[22]

However, the proposed method is not able to detect and correct for non-abrupt data production changes. For example, if a new death certificate form, impacting certification practice and final coding, slowly spreads through the population (as was the case in France over the period 1997-1999), the impact on yearly death counts would occur over several years. But, to the authors' knowledge, no general method is able to correct time-spread data production changes.

When comparable, the multiplicative factors obtained from bridge-coding studies and time-series methods were similar.[11, 15-17, 37, 38]

The purpose of this work is not to challenge bridge-coding studies. However, bridge coding studies are not implemented in all countries and it would be very difficult and costly to do so retrospectively for every data production change. The time series analysis methods proposed herein provide a reliable way of correcting data production changes affecting death count time trends.

Given the indirect manner in which data production changes are identified, the method necessitates feedback from data producers in order to confirm the plausibility of the changes and explain them. Without that additional information, the automatic method would blindly correct any detected jumps, some of which may be related to real abrupt and sustained variations in the mortality risk. However, it is not always straightforward for a data producer to obtain a broad overview of past coding process methods in the producer's country. The reasons for the occurrence of some of the oldest jumps may have been lost. Therefore, the decision to take into account or not any detected jump that is not

confirmed by the data producer will depend on the degree of confidence that the jump is not attributable to a production change.

Some jumps are of great amplitude (e.g. rheumatic heart disease). This may be observed when the cause considered is highly likely to be the result of other causes.[10, 23] In that case, the death count time trend is very sensitive to changes in coding rules (e.g. ICD10 rule 3). However, the absence of high amplitude jumps is not sufficient to ensure the interpretability of time trends. Time trends for some conditions like hypertension, heart failure and renal failure have to be interpreted cautiously. Indeed, the approach chosen was to only consider the underlying cause of death, and these specific causes may be selected as underlying, due to lack of additional information about the real underlying cause on the death certificate. In these cases, mortality time trends could be influenced by other conditions, or slowly diffused certification changes. A multiple cause approach, considering each cause mentioned on the death certificate, could bring much different results.

Large jumps may also be observed when a country uses very specific codes. In this study, for practical reasons, it was decided to use the same codes for all the countries. However, the same general method could have been applied to specific codes for each country.

In any event, time trends for causes with large amplitude jumps, even after correction, are to be interpreted with caution.

For some causes, jump amplitude was markedly heterogeneous by age. This result was already observed in bridge coding studies.[11, 16] This result could be attributed to three factors: first, for some causes, sub-cause structure is different by-age, and each sub-cause is differentially impacted by production change; second, older age mortality is more frequently associated with multiple pathologies, and the selection of one of these as the underlying cause may change with coding rules; third, in certain cases, the same death certificate may be interpreted differently depending on the age of the deceased, and this difference may also depends on the coding rules used.

The method developed in this work package was applied to the whole set of causes of death and countries. The set of causes considered is heterogeneous in terms of frequency of occurrence (e.g. more than a 100-fold difference between the frequencies of cerebrovascular disease and malignant neoplasm of the testes) and sensitivity to coding change (no sensitivity for congenital heart disease and high sensitivity for heart failure).

However, correction factors were successfully produced and used by other work packages of the AMIEHS project.

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6. Validation of avoidable mortality indicators through trends analyses (Results of work package 5)

Authors: Rasmus Hoffmann, Iris Plug, Caspar Looman, Johan Mackenbach
Affiliation: Erasmus MC, Rotterdam, The Netherlands

6.1 Introduction

The AMIEHS project uses a new approach towards the selection of indicators of amenable mortality by empirically validating possible indicators of amenable mortality. We aim at providing evidence on the effectiveness of health care interventions. In this report we describe how we study the impact of predefined innovations in health care on cause-specific mortality trends from 1970 to 2005 in seven European countries. The selection of innovations and causes of death is the result of extensive literature reviews on the effectiveness of interventions in work package 1 in this project (Chapter 2 of this report) and of extensive literature reviews on the timing of interventions in our seven countries in work package 2 (Chapter 3 of this report). In the past expert opinions and clinical evidence on which causes of death are amenable by health care interventions, and which interventions have an impact on mortality from these causes, have been the main basis for the choice of indicators for the concept of amenable mortality. Only rarely it has been empirically verified whether these interventions also show an impact on mortality on the population level.[1 2 3] However, the attempt to find empirical validation for the effectiveness of health care innovations could be an important step forward in making the concept of amenable mortality useful for routine surveillance of health care.

In the following the different approaches and methods will be described and the main results highlighted and summarized with a focus on methodological aspects. Additional figures showing mortality trends and the timing of innovations are in the appendix B. Interpretations and conclusion for the AMIEHS project as a whole will be elaborated in a separate chapter of this report.

6.2 Methods

Description of mortality trends

For all participating countries (Estonia, France, Germany-West, Germany-East, The Netherlands, Spain, Sweden and the United Kingdom) cause-specific mortality data describing the period between 1970 and 2005 were gathered by 5-year age categories and gender (see Chapter 4 of this report). Although mortality data is available for the German Democratic Republic (GDR) from 1980 to 1990 and for the eastern parts of Germany after 1990, only West-Germany is included in the analysis of the association between mortality trends and health care innovations. This is because it was not possible to find information on the introduction of innovations in health care for the GDR in WP 2. However, in cases where the mortality trend in the GDR gives additional insight into the changes in Eastern Europe around 1990, we add the description of mortality from this country to the description of Estonia.

In order to relate significant changes in the mortality trend to innovations in health care, the mortality trend pattern based on annual information needs to be simplified and described with appropriate statistical models in order to make changes between periods detectable, measurable and differences between countries comparable. This is done using joinpoint models based on linear spline regression to identify “knots” in the mortality trend that mark the years in which the mortality trend changes significantly.[4 5] We used the statistical software R. We found that three knots describe all mortality patterns sufficiently well, splitting the study period of 35 years in 4 parts. The regression model optimizes a linear spline and estimates the years (the position of the knots) that best fit the mortality trend. Numbers of death per age group were taken as the outcome variable with a Poisson distribution. The logarithm of the population size (person years at risk) was added as an offset factor to model the denominator. Besides the timing of the knots the output of this analysis also includes the Percent Annual Change (PAC) for each of the 4 periods between the knots. Based on this, it can be determined in which year the mortality trend changes significantly, and these years can be compared between countries and be related to the year of the medical innovation. The results of this descriptive first part of the analysis of mortality trends are presented in the first part of the results section.

Within the period between 1970 and 2005 several ICD-coding systems were in use. In WP 4 correction factors were developed to adjust for the influence of changes in ICD coding on the mortality trends (see Chapter 5 of this report). To take into account a possible cohort effect on the mortality trends, an age-period-cohort (APC) analysis was performed. As the outcomes of these analyses did not reveal biases due to a cohort effect, we maintained the regular analyses without control for cohort effects. After the regression, we produced figures with the mortality trend. To let these figures be comparable between countries we standardize the age distribution with the European standard population. In a first set of analyses no age limit was used. A second round repeated all steps of the analysis for the age range 0-74.

Exploring the association between mortality trends and innovations in health care

The following description explains which steps were taken to get from a description of the mortality pattern to evidence on the association between the timing of innovations in health care and mortality trends. The total number of knots (significant changes in the mortality trend) from the joint point analysis explained above is determined by the following dimensions: First, we study 14 conditions for which we do not only have data on mortality but also information on the timing of one or two relevant innovations in health care. In WP 2 this information was transformed in a period of 4 to 9 years where one would expect the influence of the innovation on mortality taking into account two time lags, one for a sufficient diffusion of a medical innovation, and one for the impact on mortality on the patient level. Second, we study 7 countries by two gender groups. For some countries we miss information on some innovations, and for other countries we can not use all mortality information (due to coding problems). Besides this some conditions only apply to men or women. Third, for each time trend three knots were identified that describe changes in the mortality trend best. From the resulting overall number of knots, we only considered those representing a favourable change in mortality, i.e. an acceleration of mortality decline, a deceleration of mortality increase, or a change from increase to decline. We only look at improvements because we only test the hypothesis that an innovation had a positive impact on mortality. We further excluded two knots where the change in the mortality trend, i.e. the change in Percent Annual Change, was not statistically significant (normally, all knots are defined as being statistically significant, but since we forced all countries to have three knots there are a few exceptions where the indicated change is not significant).

The overall number of favourable changes in mortality was 264 for the analysis of all ages, and 262 for the analysis of ages 0-74. For these knots we established if they coincide with the period where an effect on mortality of the introduction of a medical innovation, as defined in WP2, can be expected. If a knot falls within this period, this was defined as a “match” between mortality trend and information on innovations in health care, suggesting that the innovation had a positive impact on mortality. Overall we find 88 matches in the all-age analysis and 82 in the analysis restricted to ages 0-74. To conclude that a certain number of matches per sex, country and condition is valid evidence for an association between innovations in health care and mortality is a complex procedure that can be subdivided into three approaches complementing each other:

1. Statistical test: We determined whether the number of matches between favourable changes in mortality and timing of innovation is higher than the number of matches that could be expected by chance: A certain number of matches would be found even if knots and periods of expected mortality decline were randomly distributed. This statistical test was applied on the total number of matches and also separately for each cause of death. Finding reliable data on the introduction of innovation in each country was a difficult task performed in WP 2 and we had to use different data sources with varying reliability of the information (see Chapter 5 of this report). Because of these problems we performed a sensitivity analysis: We divided the data on innovation dates into more and less reliable information and repeated the statistical test for both groups.

2. Count of matches by conditions, on the level of countries: In order to reveal which of the 14 causes of death are influenced by the predefined innovations in health care, we counted the countries that show a match for a condition. If 2/3 of all countries with valid data show the association we interpreted this as evidence for an impact of the innovation on mortality.
3. Regression analysis: An OLS-regression was the last and the most formal approach to analyzing the association between the timing of innovation and favourable changes in the mortality trend. If we consider our seven countries to be the units of analysis, we would expect that the later the innovation, the later the change in the mortality trend. As input for the regression analysis we used the starting year of the expected period of the mortality decline. Using the middle year or the last year would give similar results because this does not influence the linear relationship between predictor and outcome.

6.3 Results

Description of international cause-specific trends in mortality. These trends can be seen in Figures 6.1 to 6.32 below.

Mortality from **HIV/AIDS** (Figures 6.1 and 6.2) shows steep increases in the late 1980's and early 1990s followed by a sudden decline after the mid 1990s. The trend was identical among both men and women. A very congruent mortality pattern over time across countries supports the idea that an innovation in health care may have had an influence on mortality from HIV/AIDS.
Mortality trends from **colorectal cancer** (Figures 6.3 to 6.6) are very divers, with most countries showing steep mortality decline but Spain and Estonia showing increasing mortality, altogether resulting in an international mortality convergence. While we find monotonically decreasing mortality in some countries, and also strong increases in other countries, the countries where we do observe a positive change in mortality from colorectal cancer, mostly in the early 1990s, suggest an influential common factor in these countries
Mortality trends across countries for **breast cancer** (Figures 6.7 and 6.8) show a clear inverse U-shape pattern with turning points from increasing to decreasing mortality concentrated around the year 1990. However, there are countries having this turning point much earlier, such as Sweden in the early 1970s, or much later, such as Estonia in 2000. These trends suggest that a common factor had an impact on breast cancer mortality.
For mortality from **cervical cancer** (Figures 6.9) we see a steep continuous decline in all countries, except for Spain that experienced an increase levelling off after 1989. These trends do not suggest the occurrence of an innovation in health care that had an international impact on mortality at a certain period between 1970 and 2005.
All countries show declining mortality from **testicular cancer** (Figures 6.10) with decreases starting to flatten in the 1990s. In Spain the decline is preceded by a sharp increase. No international pattern can be found that suggests the influence of a particular health care innovation.
In all countries mortality from **Hodgkin's disease** (Figures 6.11 and 6.12) has decreased throughout the study-period with several fluctuations of this decline. For example, in Germany the decline is

preceded by a short period of increasing mortality before 1980. The international pattern of mortality trends does not suggest a particular influence of a health care innovation in a certain period.

Mortality trends for **leukaemia** (Figures 6.13 and 6.14) show convergence between countries between 1970 and 1990 with some improving countries (Sweden, Netherlands) but also increasing mortality, e.g. in Spain. After 1990 there is mostly parallel decline between countries for males but mortality is increasing for females in Eastern Germany and Estonia. The trends suggest that influencing factors in the late 1980s have made the trend more similar across countries afterwards.

Mortality from **rheumatic heart disease** (Figures 6.15 and 6.16) declined steeply in most countries in the 1970s. In France and Estonia the mortality only started to fall in the 1980s. In these two countries the decline was followed by a short period of increase. There is no time pattern for mortality across countries that suggests a common factor behind the observed mortality declines.

In almost all countries mortality from **hypertension** (Figures 6.17 and 6.18) decreased in the 1970s, and in some countries it increased again in the 1990s resulting in a U-shaped trend in mortality. In France mortality from hypertension has increased, followed by a sharp decrease in the late 1980's. In Estonia a very limited decline of mortality was observed followed by a sharp increase after 1995. This pattern does not suggest a common effect of an innovation in health care on mortality from hypertension in different countries.

In many European countries, mortality from **ischemic heart disease** (Figures 6.19 to 6.22) has declined since the 1970's but with variations in the speed of mortality decline. This decline was preceded by an increase in some countries. This change from increase to decrease in some countries supports the idea that a health care innovation may have been associated with this change.

Mortality from **heart failure** (Figures 6.23 and 6.24) steeply decreased in the 1970s in most countries, but the decline slowed down in later decades, and in some countries periods of decreasing mortality alternate with periods of increasing mortality. The observed pattern does not suggest a particular period where an innovation in health care had a decisive influence on mortality.

In all countries mortality from **cerebrovascular disease** (Figures 6.25 to 6.28) has strongly decreased throughout the study-period from 1970 to 2005 with several fluctuations of this decline. The only exception is Estonia where mortality was almost stable and even increasing for men until 1993, followed by a steep decline. Due to its general decline, the observed pattern does not suggest a particular period where an innovation in health care had a decisive influence on mortality, except for Estonia where a clear change of the trend is observed in the early 1990s. This change could also be due to general social and economic changes during this period in Eastern Europe. This is confirmed by the trend in Eastern Germany where we see a stable or even increasing level in the 1980s and a clear downward trend after 1990.

In most countries mortality from **peptic ulcer** (Figures 6.29 and 6.30) has decreased throughout the study-period. Only for women in the UK and France there was a steep increase until the early 1980s followed by a steep decline. In Estonia a spiky pattern is observed with a sharp increase followed by a sharp decline in mortality. The pattern in these three countries suggests a clear change of mortality in a certain period but we are uncertain whether these changes can be related to an innovation in health care.

Mortality trends from **renal failure** (Figures 6.31 and 6.32) are very diverse across countries with increasing and decreasing trends, as well as countries with a peak in mortality in the 1980s. From these trends we can not conclude on an innovation in health care that would have an international impact on mortality from this cause of death.

In the following, Figure 6.1 to 6.32 show standardized cause-specific all-age mortality trends by gender for the countries under study and, just below the lines for the mortality trend, lines for the periods of expected mortality declines. (The same graphs for the age-range 0-74 and the detailed national graphs with statistical information for both age ranges can be found in appendix B). On top of each graph there is the cause of death, gender (M or F) and the innovation.

Figure 6.1: Standardized all-age mortality trend from HIV/AIDS for men and expected period of mortality decline based on timing of introduction of anti-retroviral drugs

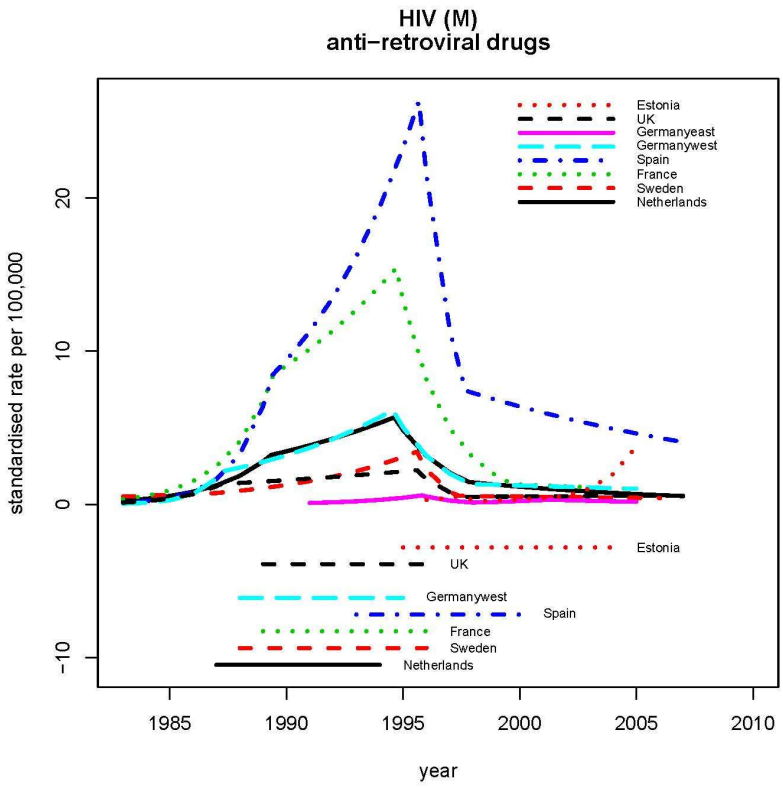


Figure 6.2: Standardized all-age mortality trend from HIV/AIDS for women and expected period of mortality decline based on timing of introduction of anti-retroviral drugs

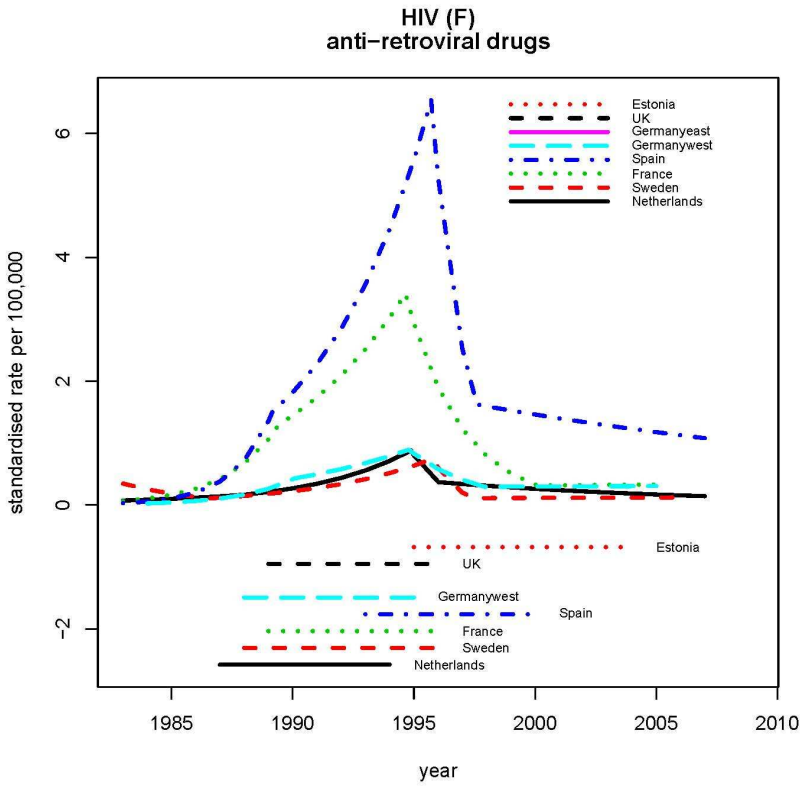


Figure 6.3: Standardized all-age mortality trend from malignant colorectal neoplasm for men and expected period of mortality decline based on timing of introduction of colonoscopy

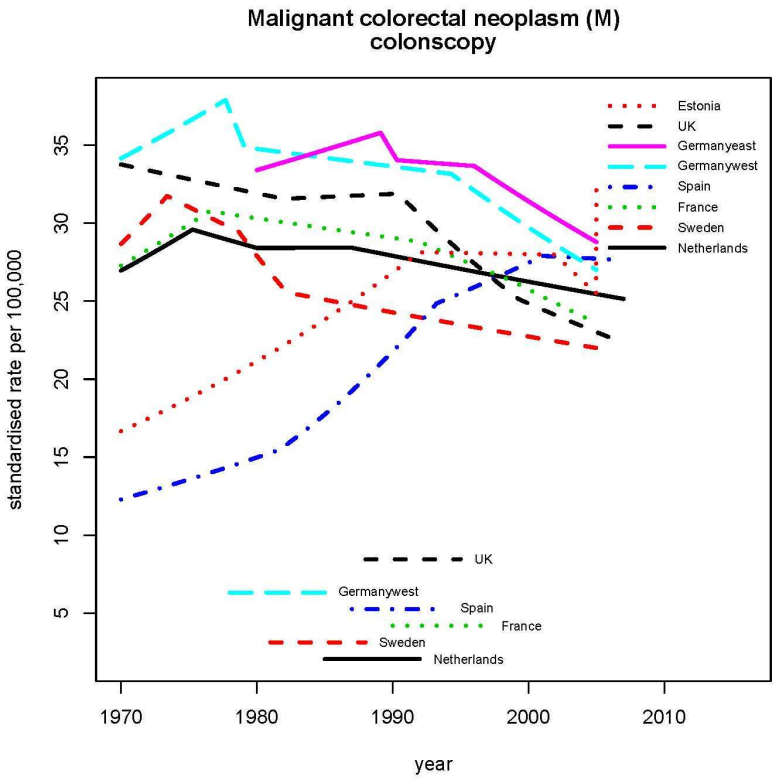


Figure 6.4: Standardized all-age mortality trend from malignant colorectal neoplasm for women and expected period of mortality decline based on timing of introduction of colonoscopy

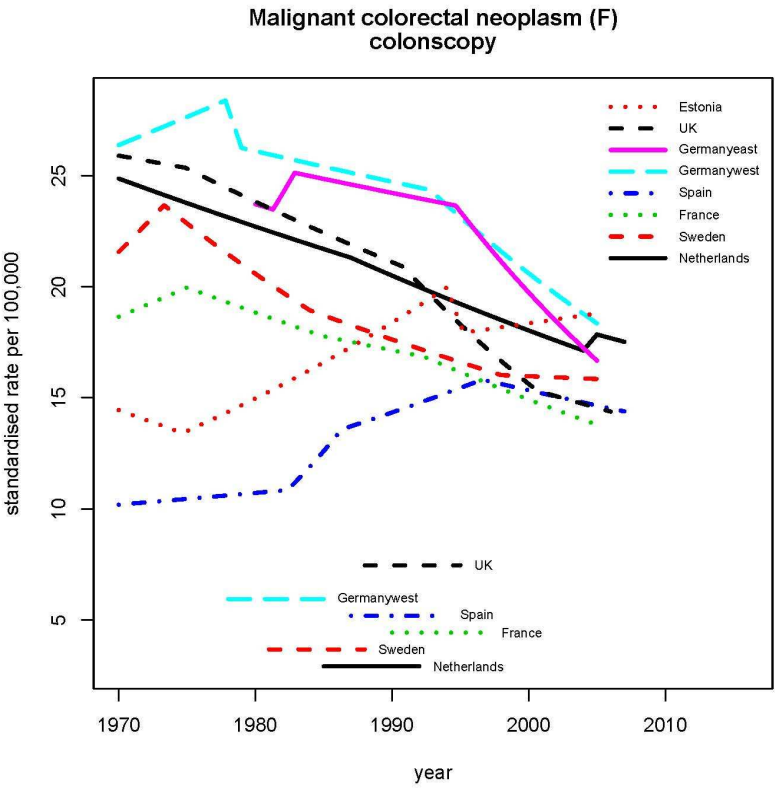


Figure 6.5: Standardized all-age mortality trend from malignant colorectal neoplasm for men and expected period of mortality decline based on timing of introduction of oxaliplatin

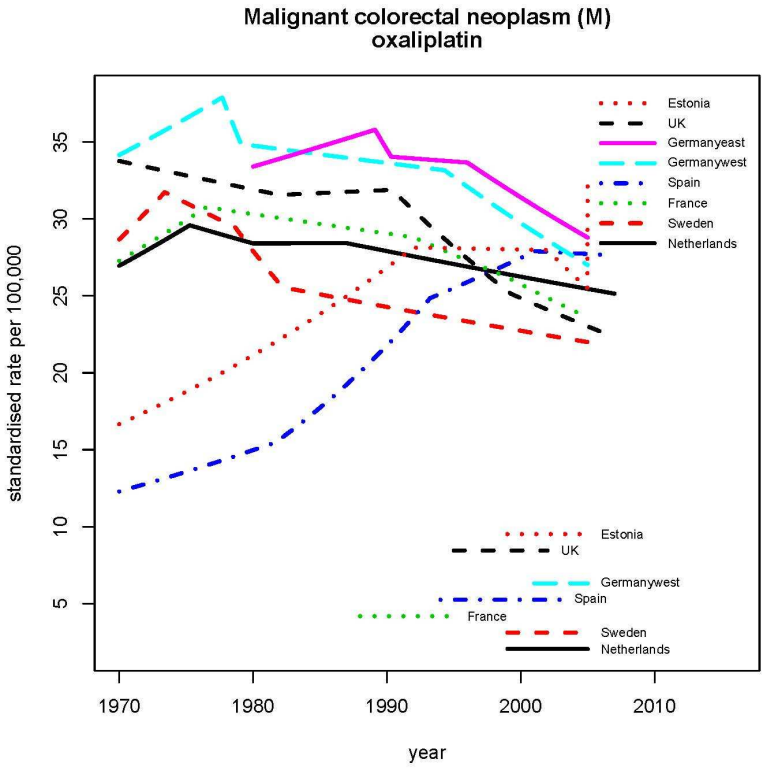


Figure 6.6: Standardized all-age mortality trend from malignant colorectal neoplasm for women and expected period of mortality decline based on timing of introduction of oxaliplatin

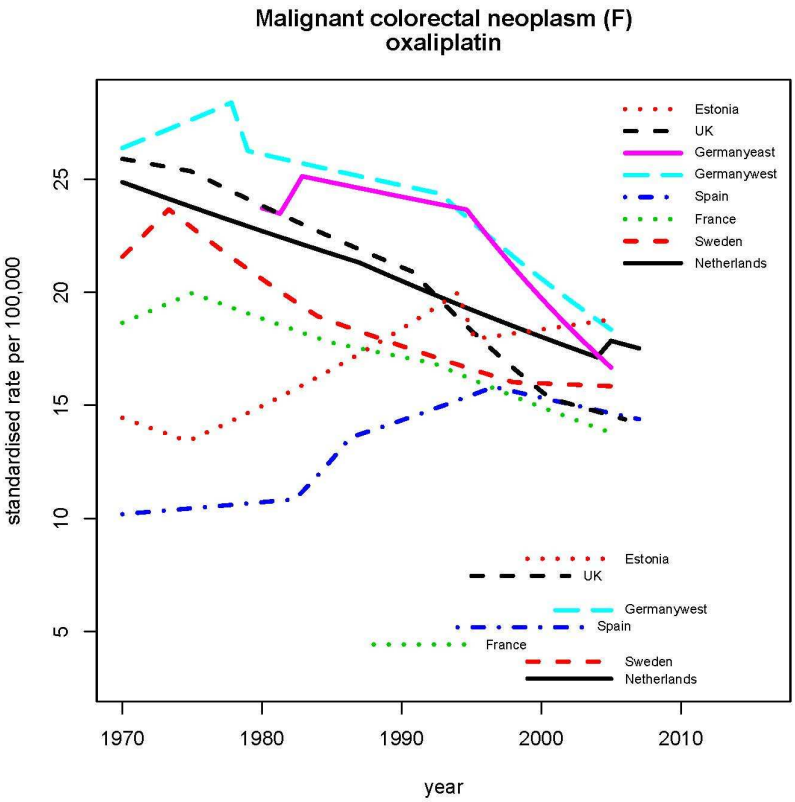


Figure 6.7: Standardized all-age mortality trend from malignant neoplasm of breast for women and expected period of mortality decline based on timing of introduction of mammography

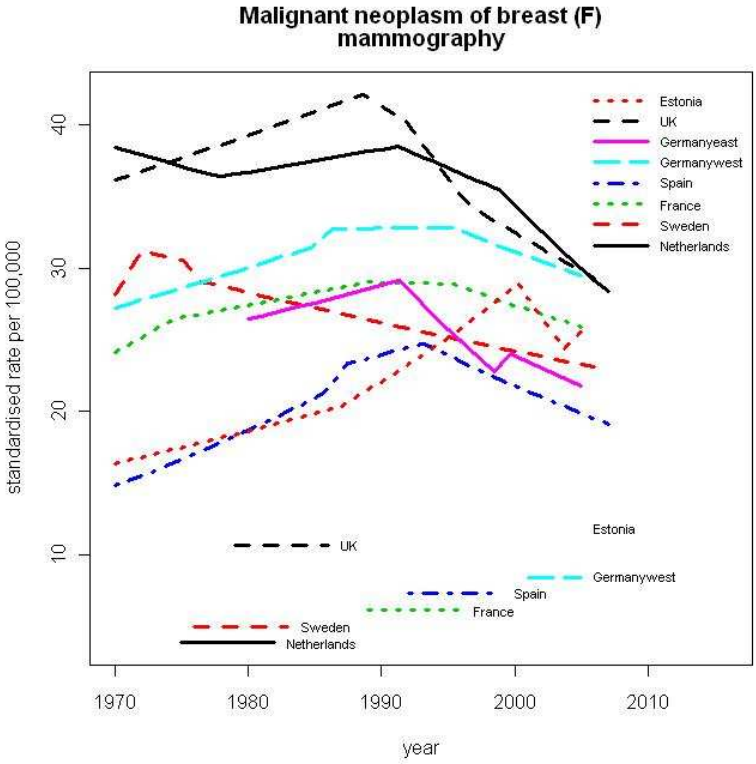


Figure 6.8: Standardized all-age mortality trend from malignant neoplasm of breast for women and expected period of mortality decline based on timing of introduction of Tamoxifen

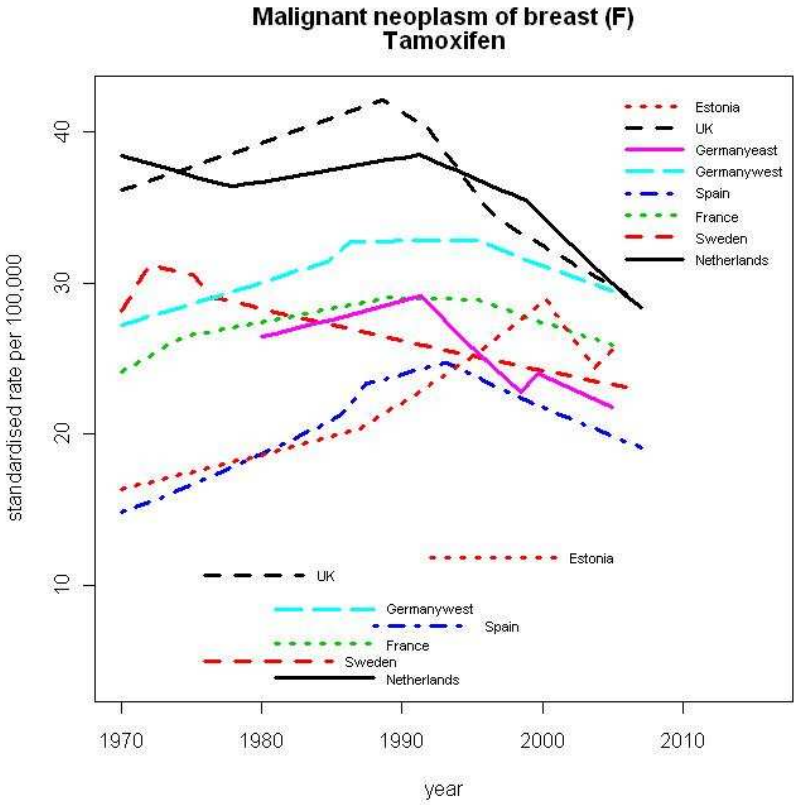


Figure 6.9: Standardized all-age mortality trend from malignant neoplasm of cervix uteri and expected period of mortality decline based on timing of introduction of cervical screening

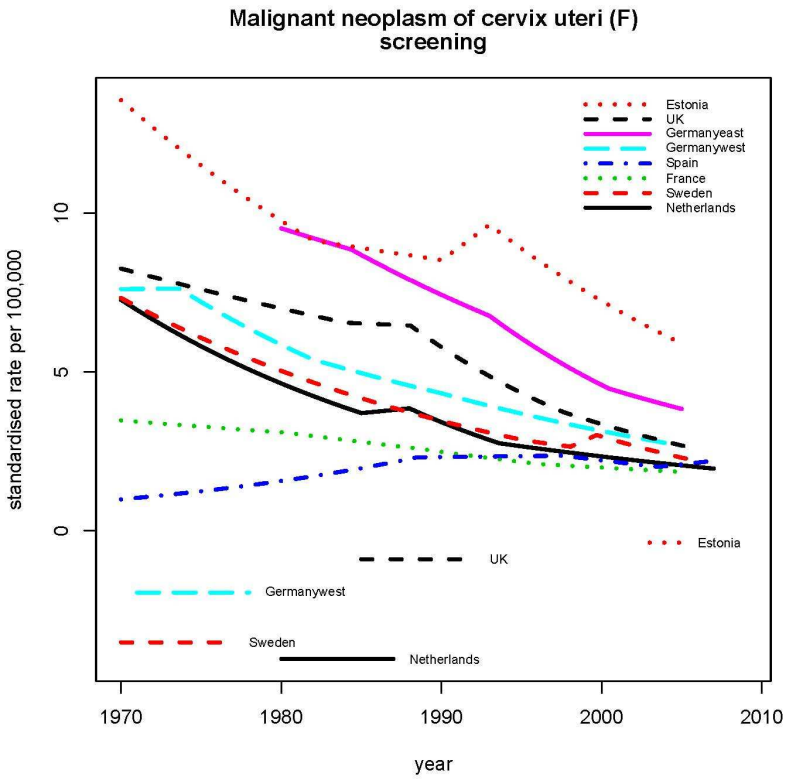


Figure 6.10: Standardized all-age mortality trend from malignant neoplasm of testes and expected period of mortality decline based on timing of introduction of Cisplatin

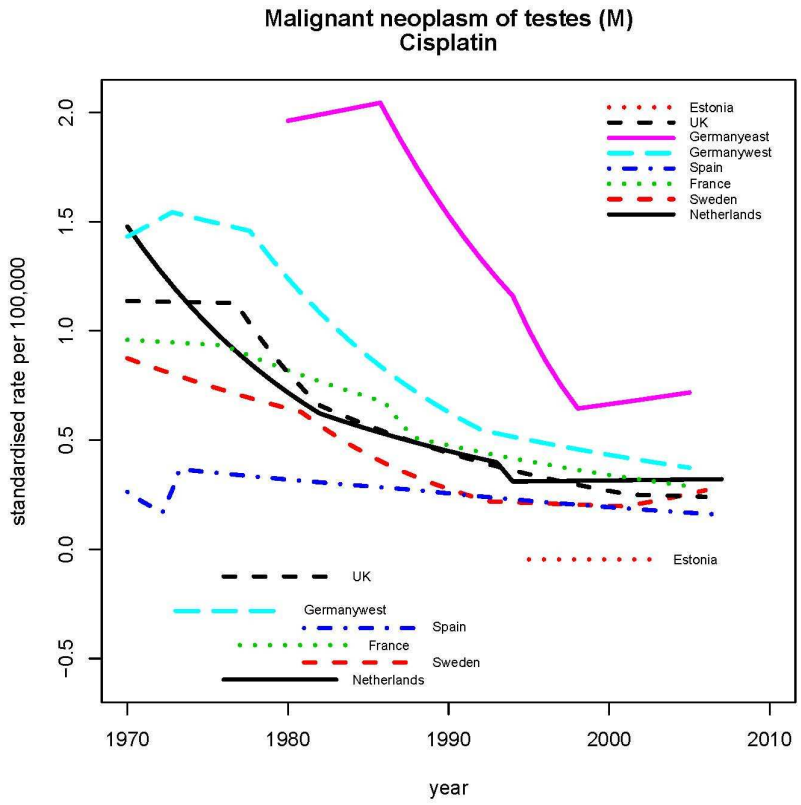


Figure 6.11: Standardized all-age mortality trend (Hodgkin's disease, men) & expected period of mortality decline based on the introduction of high dose therapy/stem cell transplantation

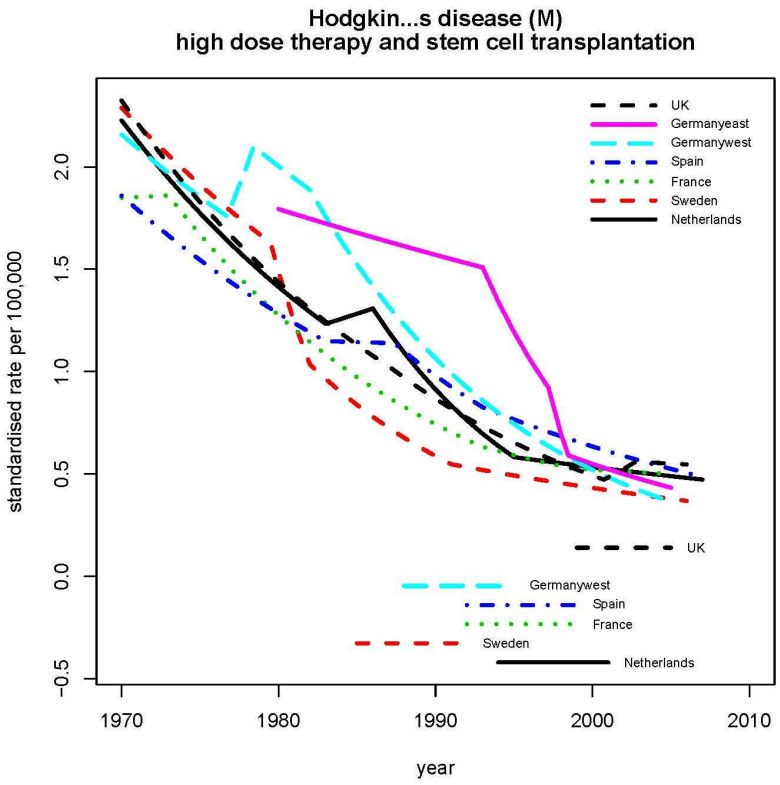


Figure 6.12: Standardized all-age mortality trend (Hodgkin's disease, women), expected period of mortality decline based on the introduction of high dose therapy/stem cell transplantation

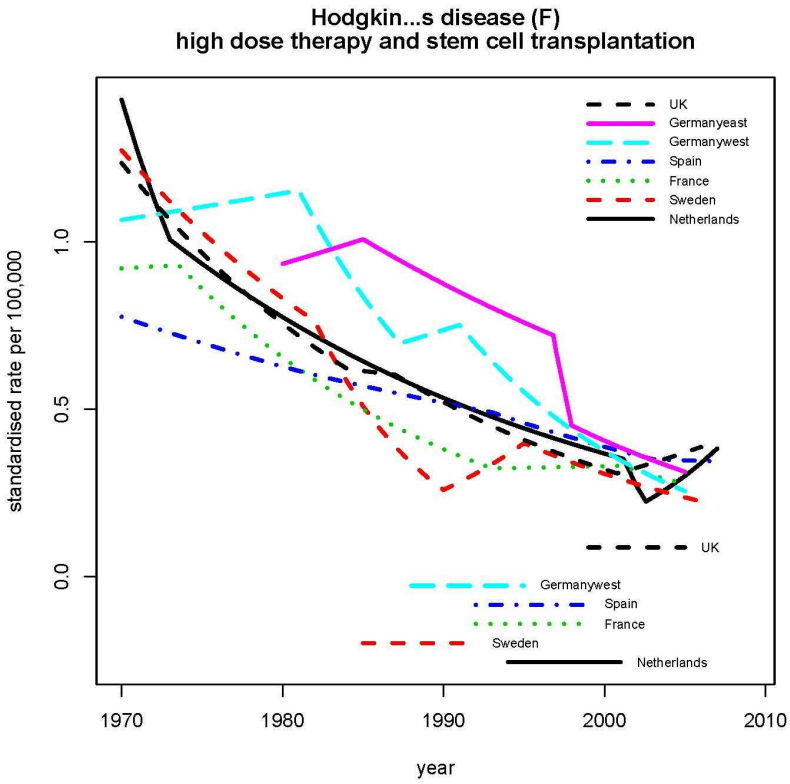


Figure 6.13: Standardized all-age mortality trend from leukaemia for men and expected period of mortality decline based on timing of introduction of improved treatment

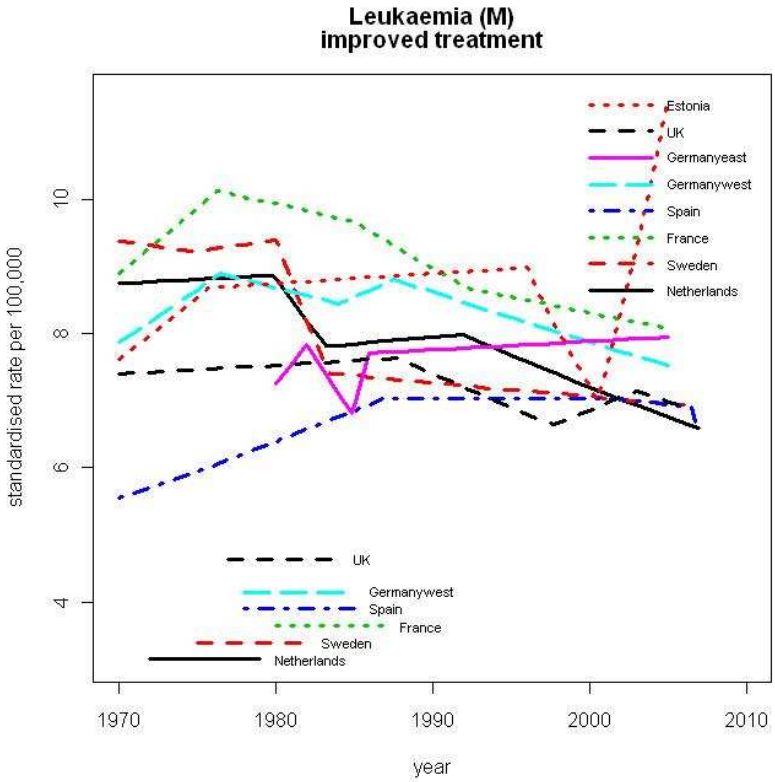


Figure 6.14: Standardized all-age mortality trend from leukaemia for women and expected period of mortality decline based on timing of introduction of improved treatment

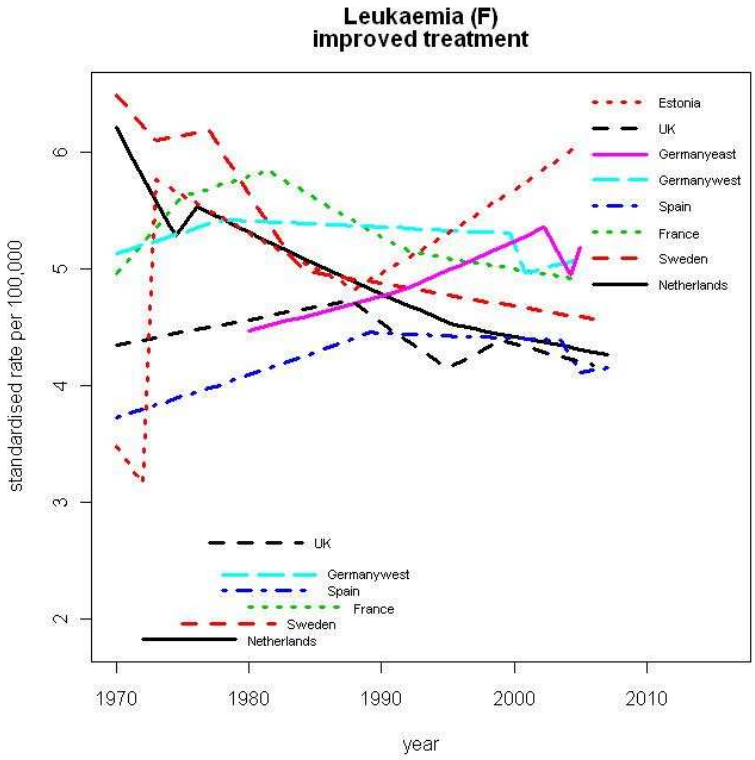


Figure 6.15: Standardized all-age mortality trend (rheumatic heart disease, men) and expected period of mortality decline based on timing of introduction of artificial valve replacement

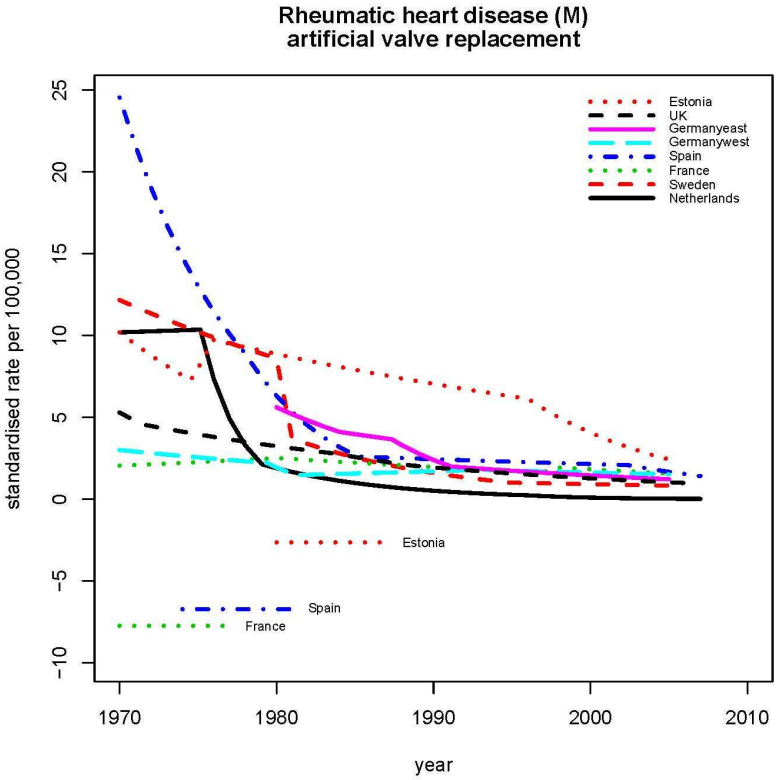


Figure 6.16: Standardized all-age mortality trend (rheumatic heart disease, women) and expected period of mortality decline based on the introduction of artificial valve replacement

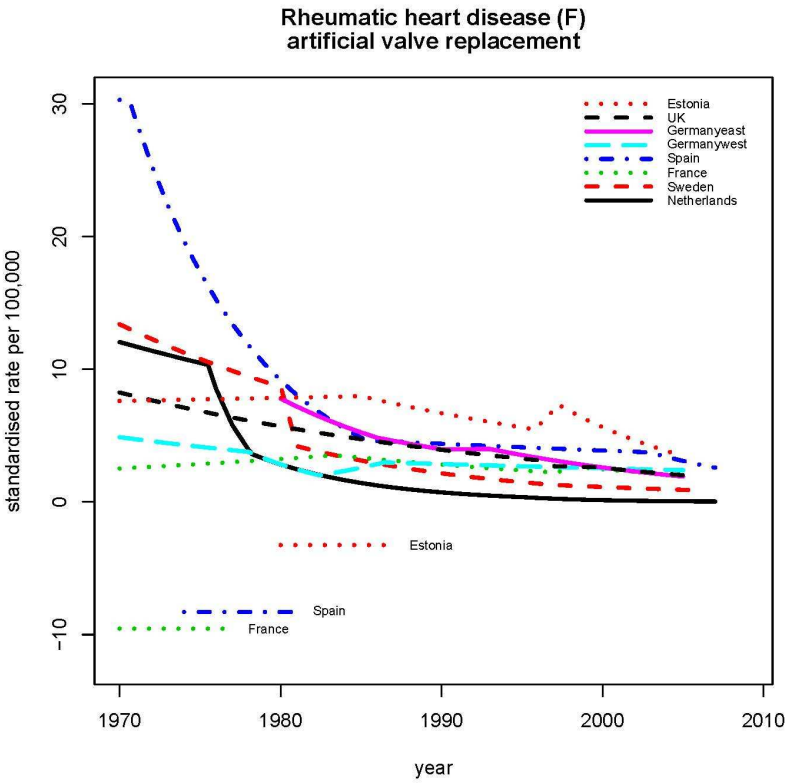


Figure 6.17: Standardized all-age mortality trend from hypertension for men and expected period of mortality decline based on timing of an increased number of patients

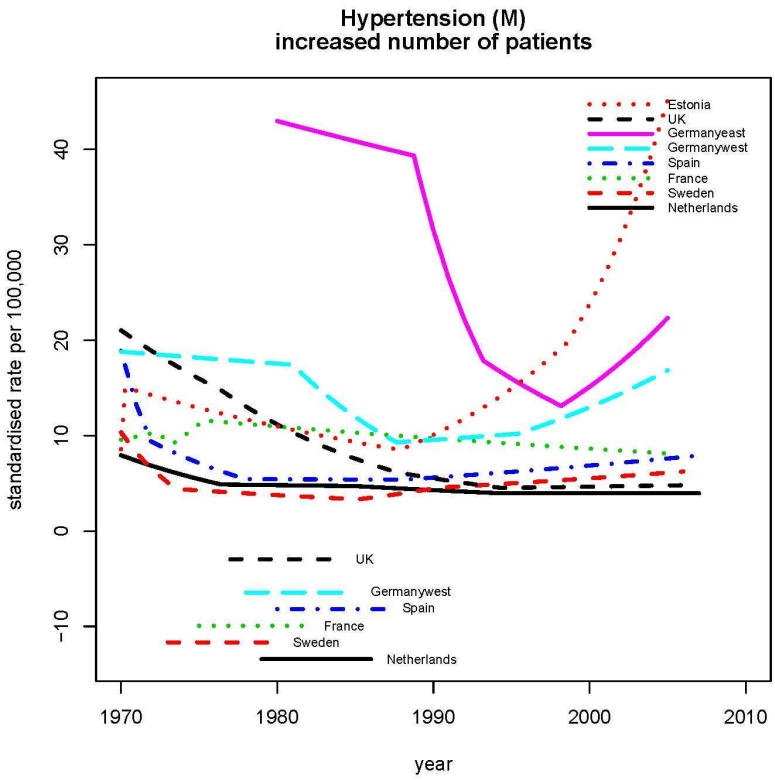


Figure 6.18: Standardized all-age mortality trend from hypertension for women and expected period of mortality decline based on timing of an increased number of patients

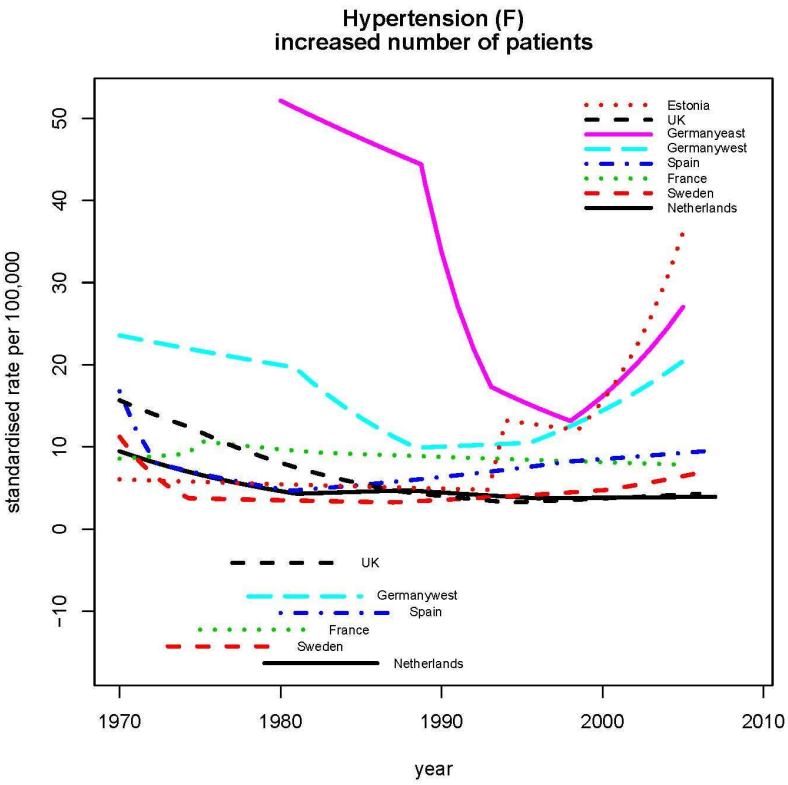


Figure 6.19: Standardized all-age mortality trend from ischaemic heart disease for men and expected period of mortality decline based on timing of introduction of betablockers

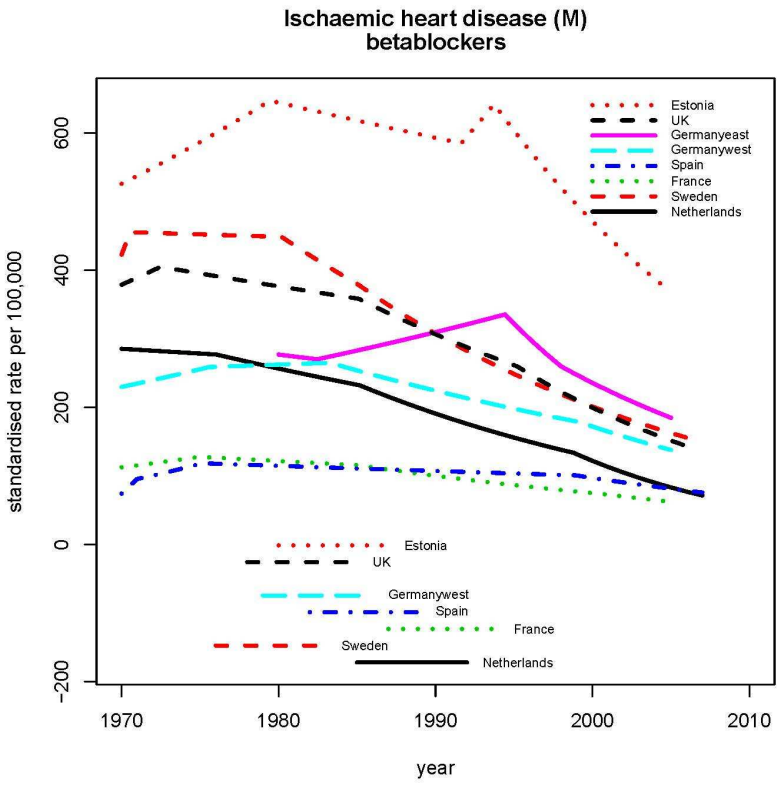


Figure 6.20: Standardized all-age mortality trend from ischaemic heart disease for women and expected period of mortality decline based on timing of introduction of betablockers

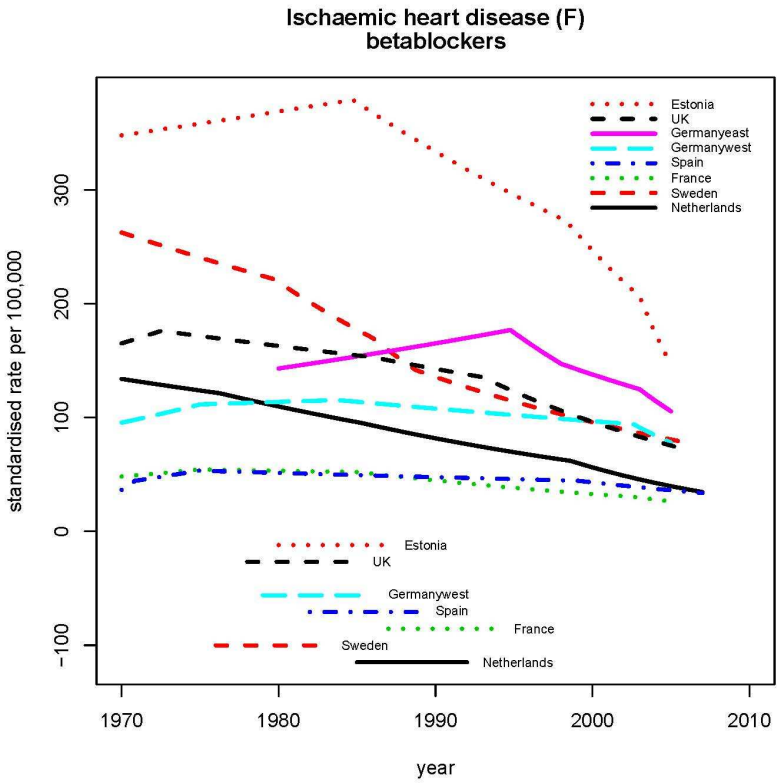


Figure 6.21: Standardized all-age mortality trend from ischaemic heart disease for men and expected period of mortality decline based on timing of introduction of coronary care units

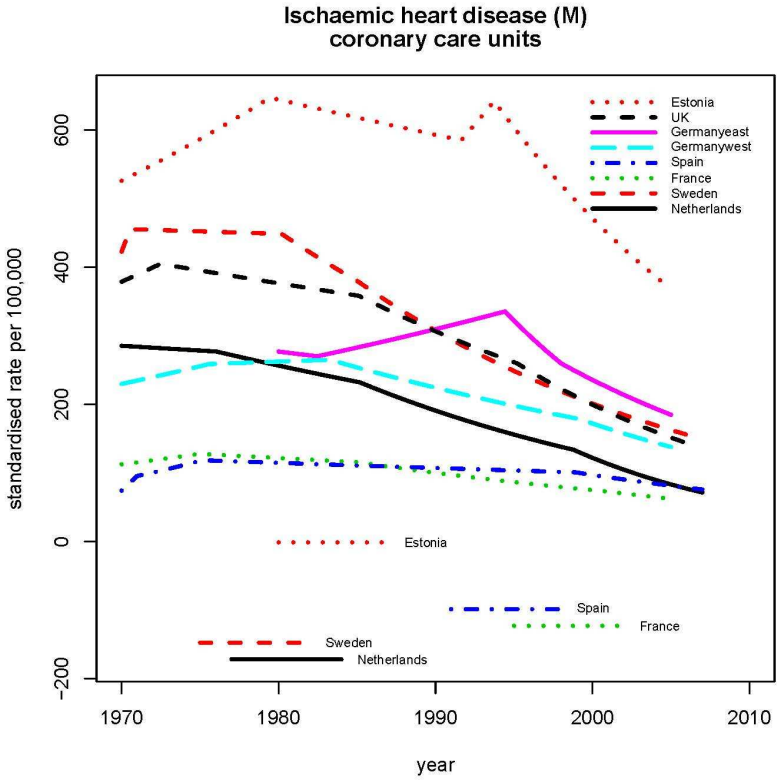


Figure 6.22: Standardized all-age mortality trend from ischaemic heart disease for women and expected period of mortality decline based on timing of introduction of coronary care units

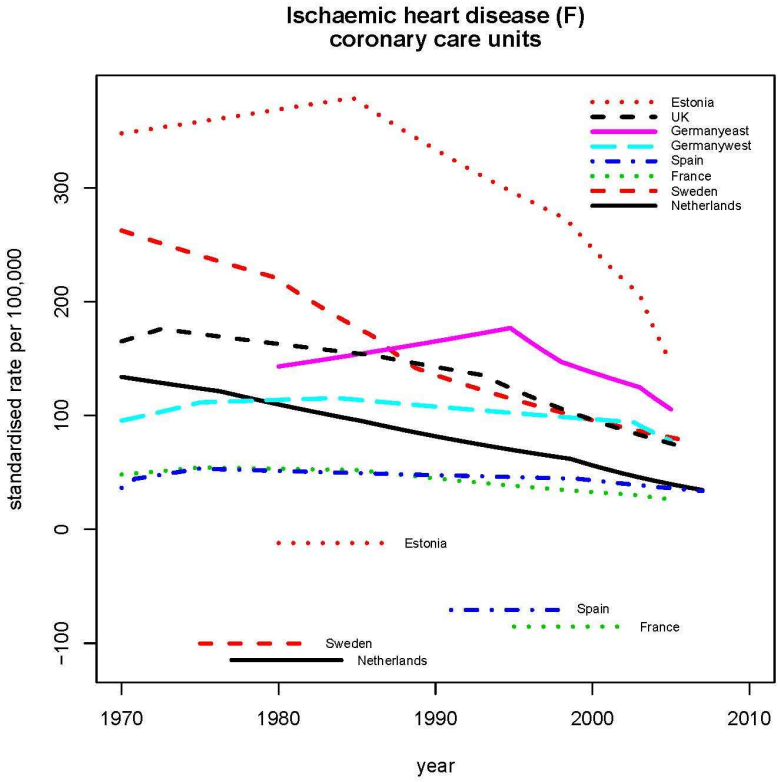


Figure 6.23: Standardized all-age mortality trend from heart failure for men and expected period of mortality decline based on timing of introduction of ACE inhibitors

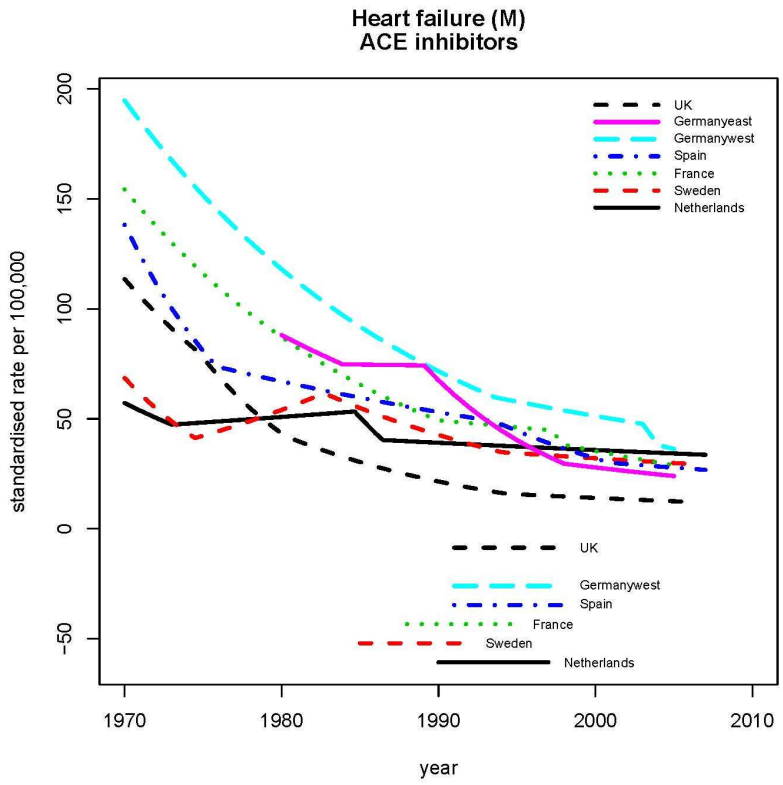


Figure 6.24: Standardized all-age mortality trend from heart failure for women and expected period of mortality decline based on timing of introduction of ACE inhibitors

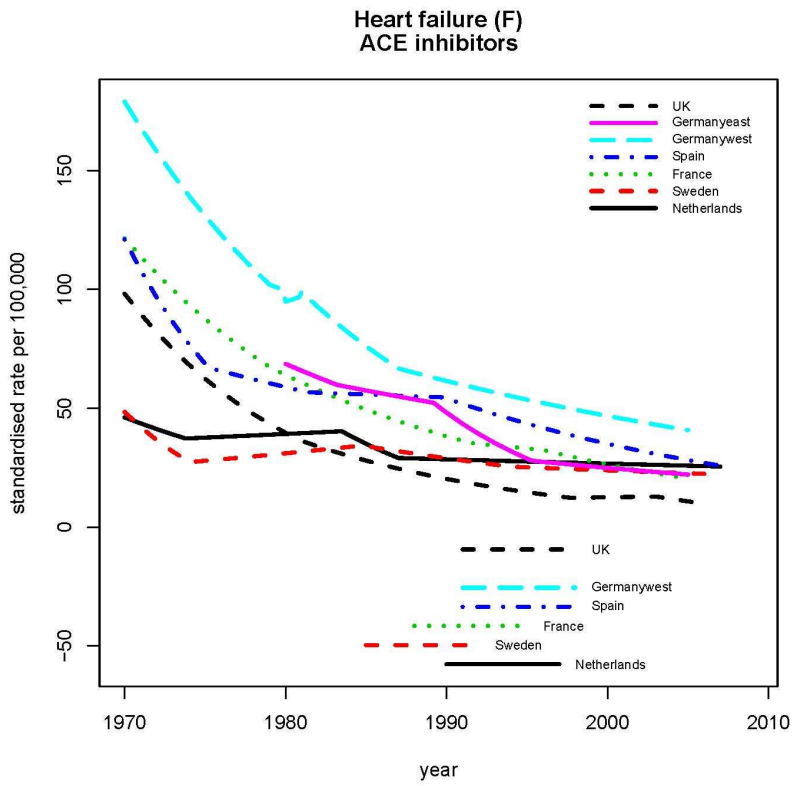


Figure 6.25: Standardized all-age mortality trend (cerebrovascular disease, men) & expected period of mortality decline based on introduction of prevention by treatment of hypertension

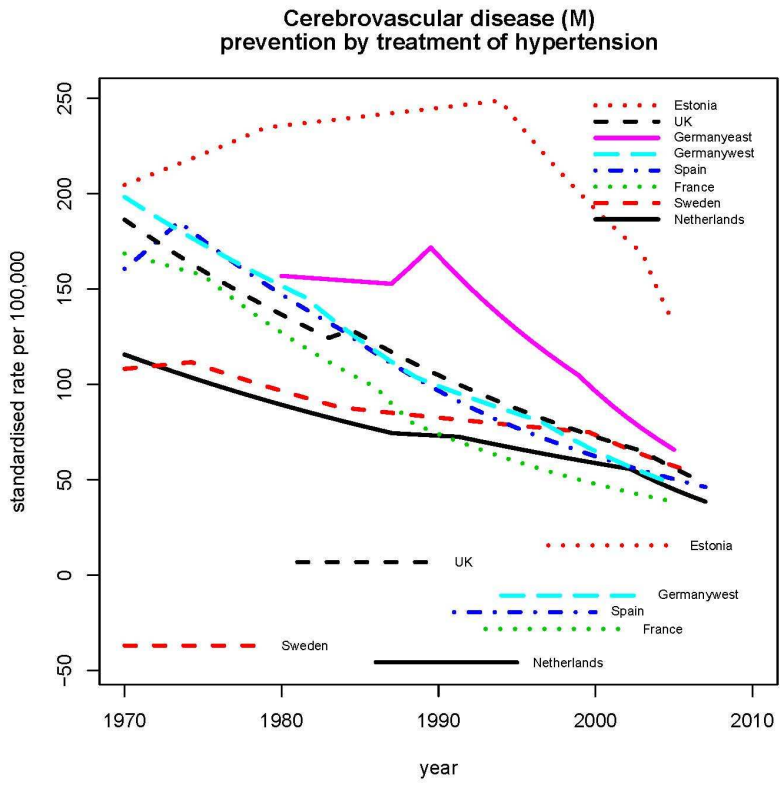


Figure 6.26: Standardized all-age mortality trend (cerebrovascular disease, women) & expected period of mortality decline based on introduction of prevention by treatment of hypertension

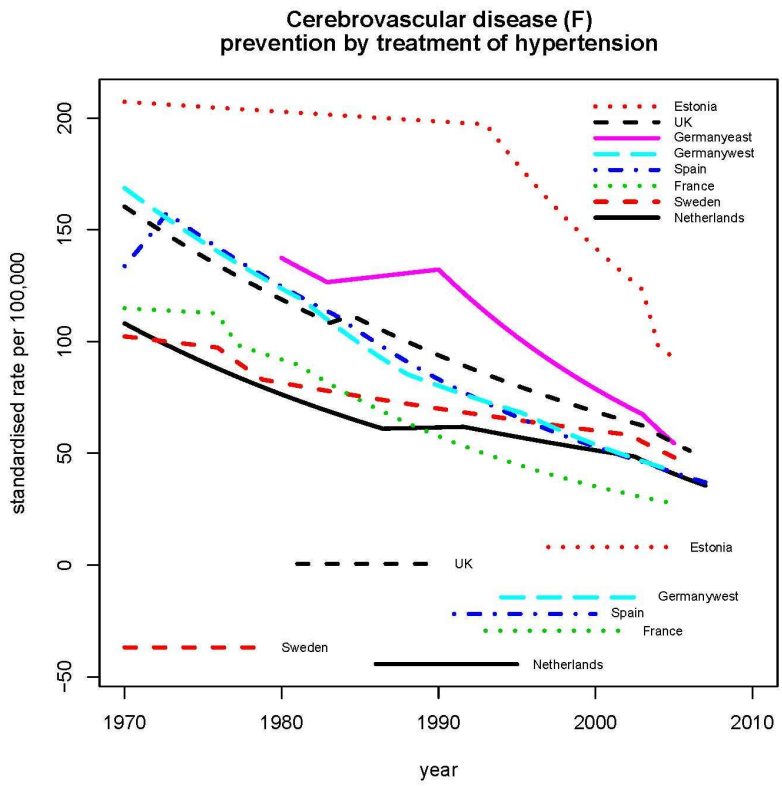


Figure 6.27: Standardized all-age mortality trend from cerebrovascular disease for men and expected period of mortality decline based on timing of introduction of intensive management

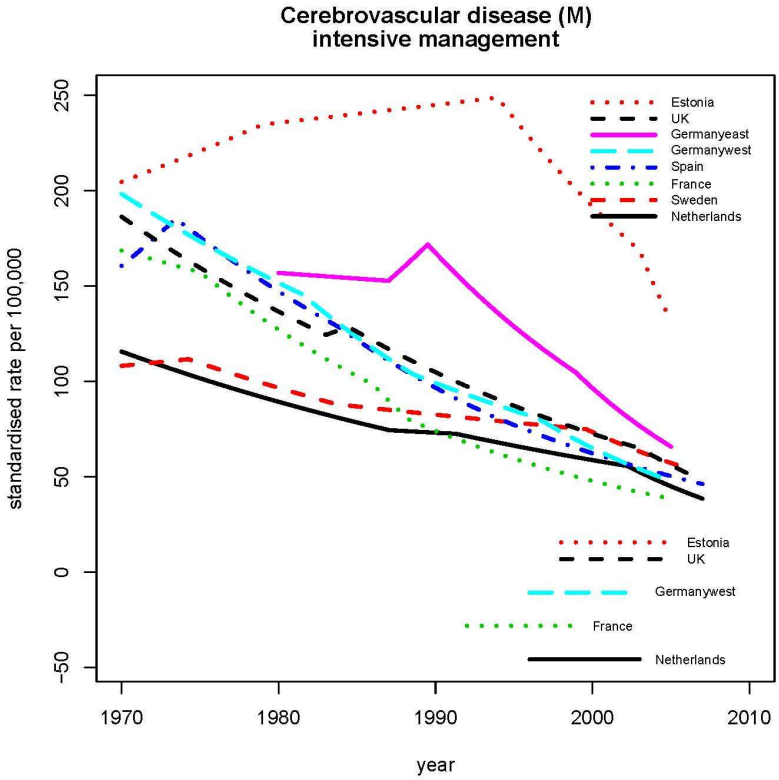


Figure 6.28: Standardized all-age mortality trend from cerebrovascular disease for women and expected period of mortality decline based on timing of introduction of intensive management

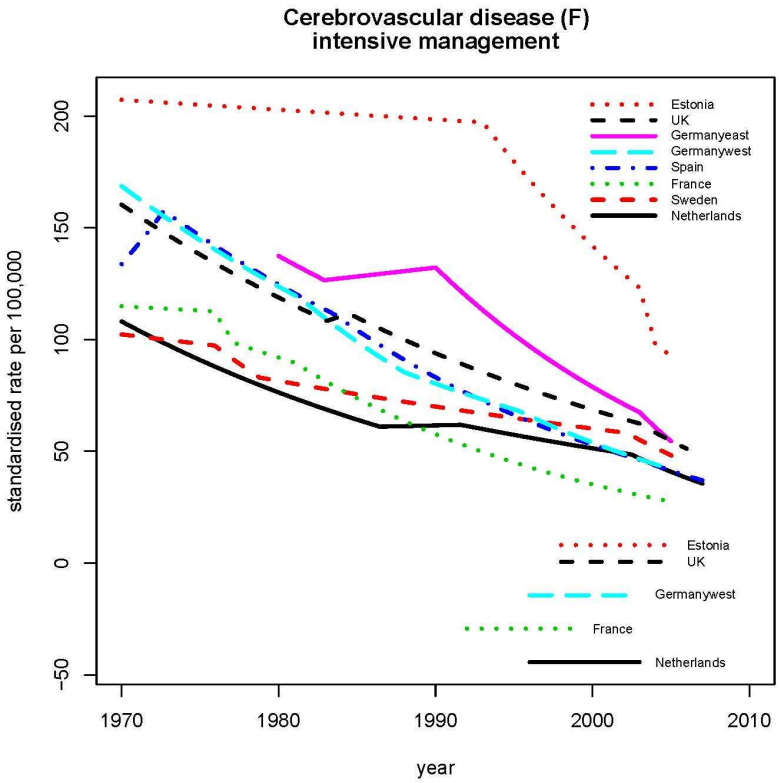


Figure 6.29: Standardized all-age mortality trend from peptic ulcer for men and expected period of mortality decline based on timing of introduction of Cimetidine

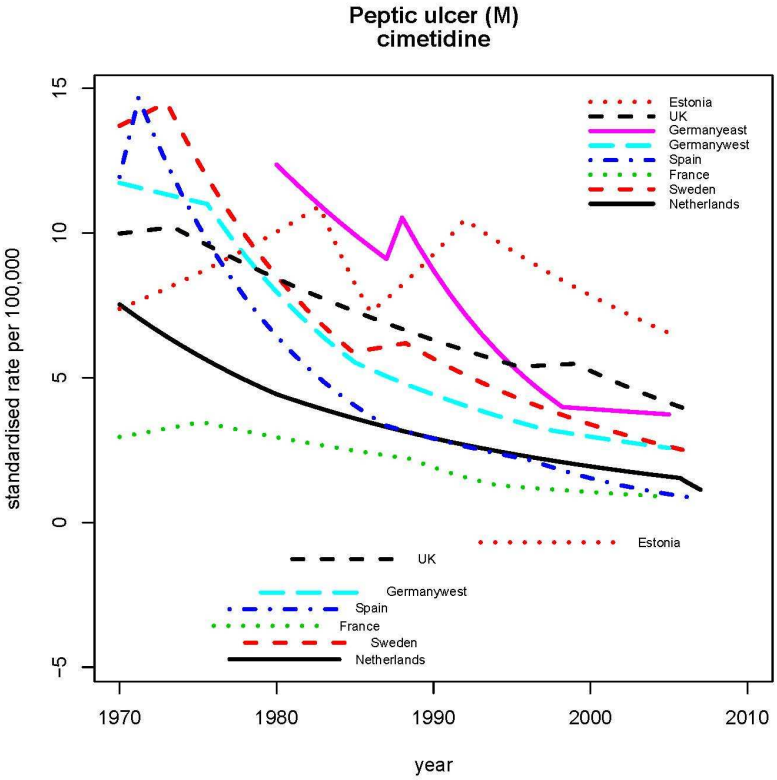


Figure 6.30: Standardized all-age mortality trend from peptic ulcer for women and expected period of mortality decline based on timing of introduction of Cimetidine

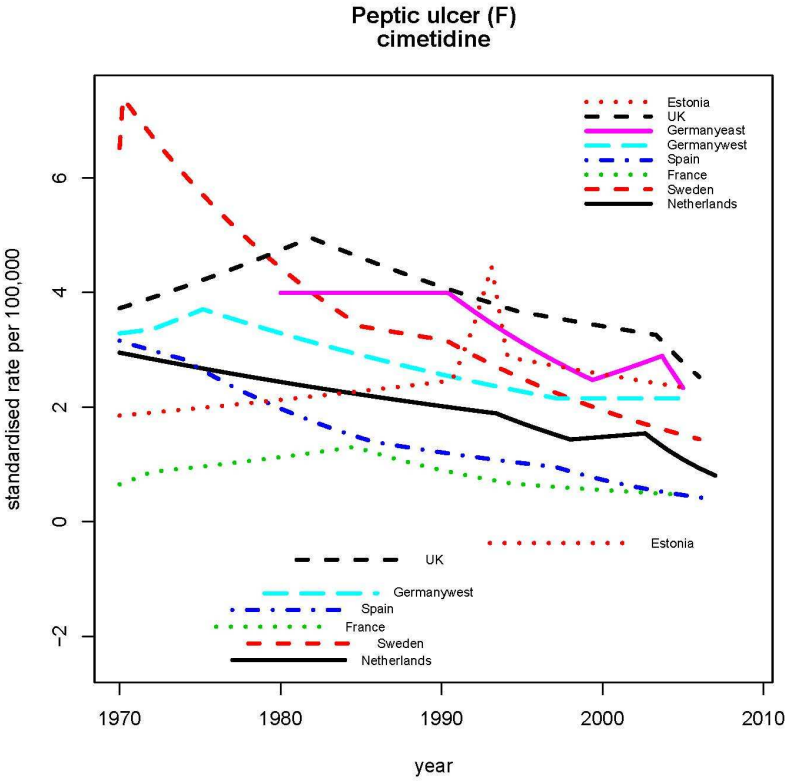


Figure 6.31: Standardized all-age mortality trend from renal failure for men and expected period of mortality decline based on timing of introduction of Cyklosporin

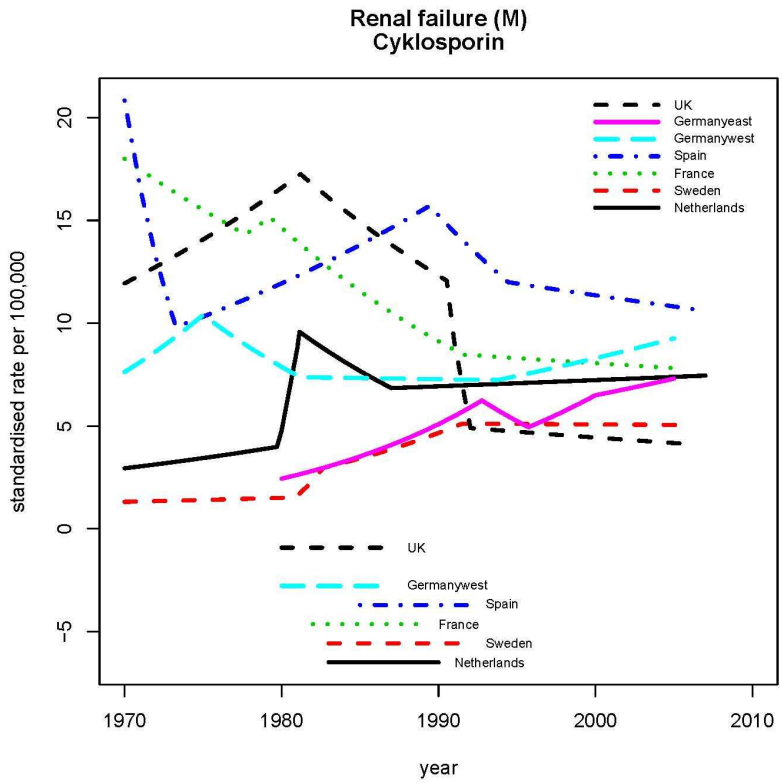
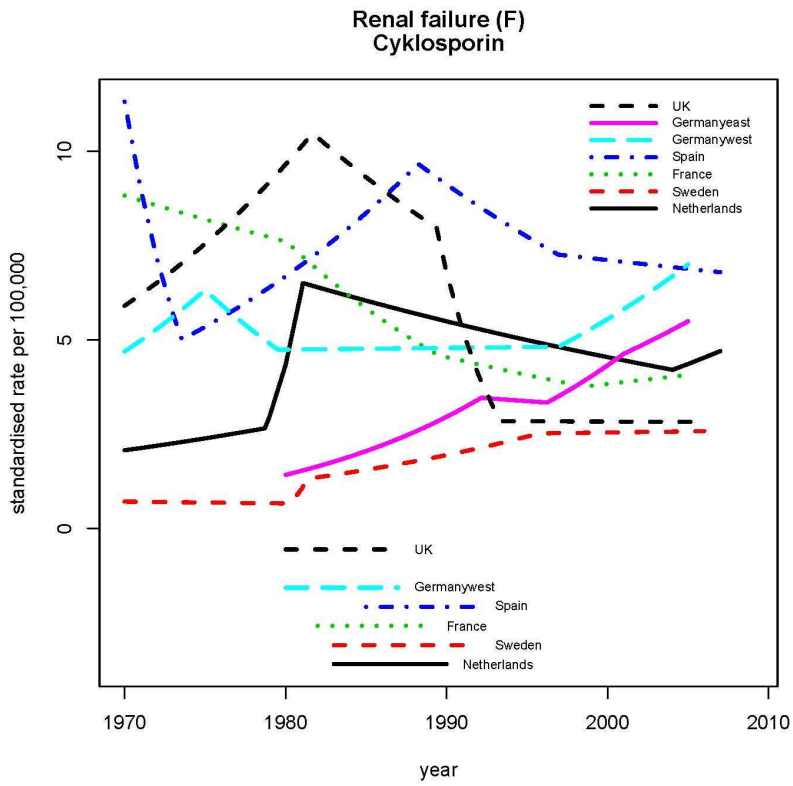


Figure 6.32: Standardized all-age mortality trend from renal failure for women and expected period of mortality decline based on timing of introduction of Cyklosporin



Association between mortality trends and innovations in health care

1. Statistical test

We calculated the likelihood to find the number of 88 matching knots (82 knots for the second analysis of the age range 0-74) assuming that the knots are randomly distributed in time, and given that an expected period for the mortality decline with an average length of about 7.1 years is located somewhere in the observation period of 35 years. This likelihood is p=0.02 for the analysis of all ages and p=0.07 for the ages 0-74 (Table 6.1). This means that the assumption of a random distribution can just be rejected, depending on the threshold for significance one wants to apply. This test shows that the number of matches found in our analysis seems to be higher than would be the case by pure chance. However, we have to deal with only borderline significance.

The differences of the results between the two age groups are opposite to what we expected: The prediction of when health care innovations should have lowered mortality is less successful for ages 0-74 than for all ages. This is surprising given the common assumption that amenable causes of death are only amenable up to a certain age, and that care is more effective in younger than in older ages.

Table 6.1 Test for the likelihood of the number of matches

	ALL AGES			AGES 0-74		
	All innovation data	Better innovation data	Poorer innovation data	All innovation data	Better innovation data	Poorer innovation data
Average length of expected period in years	7.16	7.13	7.16	7.13	7.12	7.14
Length of the observation period	35	35	35	35	35	35
Number of favourable knots	350[a]	170[a]	180[a]	345[a]	170[a]	175[a]
Theoretical chance of a match	0.20	0.20	0.20	0.20	0.20	0.20
Expected number of matches	71	35	37	70	35	36
Actual number of matches	88	46	42	82	45	37
Observed probability of a match	0.25	0.27	0.23	0.24	0.26	0.21
p-value for the difference between theoretical and observed chance (1-sided Chi-square test)	0.020	0.026	0.174	0.070	0.036	0.401

[a] The favourable knots for conditions where we have two medical innovations have to be counted twice because they have a double chance to match with a period of expected mortality decline.

The separate statistical test for each cause of death reveals that for all ages only the prediction of mortality decline for HIV is significantly better than a random prediction, and for ages 0-74 we find significant results for HIV and cerebrovascular diseases. It should be mentioned that the statistical power of an analysis for a separate cause of death is low and so is the chance that the number of matches found is significantly higher than the number of matches expected by chance.

Table 6.1 also shows the results of the sensitivity analysis based on a ranking of the information on innovation dates into “better” and “poorer” quality. The results show that the innovation data based on more reliable sources are more likely to show an association with the mortality trends (for both age

groups the p-value is below 0.05), whereas the expected periods based on poorer data do not show a significant association with mortality trends.

2. Counts of matches on the level of countries

Our main criteria for defining evidence of an effect of health care innovations on mortality is the count of countries that show an association between health care and mortality. We counted the number of countries (1) where we found a match for both sexes, (2) where we found a match for only one sex, and (3) where we found no match. For some conditions either data on mortality could not be used or data on innovations were unavailable, therefore the total number of countries that could be taken into account is sometimes less than 7 (Table 6.2). This perspective at the country level emphasizes the internationally comparative approach and suggests four possible indicators for amenable mortality, for which more than 2/3 of the valid countries show a match. For all ages these conditions are HIV, colorectal cancer, ischaemic heart disease and cerebrovascular disease. For ages 0-74 these are HIV, leukaemia, rheumatic heart disease, hypertension and cerebrovascular disease. Thus, only HIV and CVD is validated in both age groups.

Table 6.2: Counts of matches on the country level

		All ages					Ages 0-74				
		Number of countries where									
Condition	**Intervention**	**2 sexes match**	**1 sex matches**	**no match**	**no data**	**association?**	**2 sexes match**	**1 sex matches**	**no match**	**no data**	**association?**
HIV	Antiretroviral treatment	4	3	0	0	**yes**	4	3	0	0	**yes**
Malign. colorectal neoplasm	Colonscopy	3	1	2	1	**yes**	3	0	3	1	no
	Oxaliplatin treatment	2	1	4	0	no	1	2	4	0	no
Malign. neoplasm of cervix uteri	Introduction cervical screening	NA	2	3	2	no	NA	2	3	2	no
Hodgkins disease	High dose therapy and peripheral blood stem cell transplantation	0	3	3	1	no	0	2	4	1	no
Malign. Neoplasm of breast	Mammography	NA	2	5	0	no	NA	3	4	0	no
	Tamoxifen	NA	3	4	0	no	NA	3	4	0	no
Malign. neoplasm of testes	Treatment with cisplatin	NA	2	5	0	no	NA	2	5	0	no
Leukaemia	Improved treatment	2	1	4	1	no	1	4	1	1	**yes**
Rheumatic heart disease	Artificial valve replacement	0	2	1	4	no	0	3	0	4	**yes**
Hypertension	Increased number of patients treated	2	0	4	1	no	2	2	2	1	**yes**
Ischaemic heart disease	B-blockers	4	1	2	0	**yes**	3	1	3	0	no
	Coronary care units	2	2	1	2	yes	1	2	2	2	no
Heart failure	ACE inhibitors	0	1	5	1	no	1	1	4	1	no
Cerebrovascular disease	Treatment of hypertension	5	0	2	0	**yes**	3	2	2	0	**yes**
	Intensive management	3	1	1	2	**yes**	1	3	1	2	**yes**
Peptic ulcer	Cimetidine	0	2	5	0	no	0	1	6	0	no
Renal failure	Cyclosporin	2	1	3	1	no	1	1	4	1	no

3. Regression

The regression used the year of the introduction of the innovation as predictor for the year of the knot in which a favourable change in mortality occurs. The assumption is that countries with a later innovation year would also show a later improvement of mortality. In order to calculate a regression model, we had to apply some simplifications to the data. First, for countries where we find a match, it was obvious which of the three knots to be included into the regression. But for the countries where we do not find a match we had to choose which of the three knots to include in the regression. Although we applied the rule of choosing the subsequent knot after the assumed period of mortality decline, this procedure left a certain degree of arbitrariness, e.g. in cases where there were no subsequent knots. Second, we run a regression that includes men and women as two cases for each country. This could be a violation of the rule that the errors in the regression should not be correlated, which in fact they are because men and women in one country have the same expected periods of mortality decline and also mostly a very similar timing of the knots. However, we used a procedure to control for this auto-correlation in SPSS.

Table 6.3 shows the results of the regression for both age groups. More than half of the results are consistent with the results that were obtained in the previous approaches above. Besides confirming three candidates for amenable mortality indicators from step 2 (HIV, IHD (Beta blockers) and CVD (both innovations) the regression for all ages combined also suggests a correlation for breast cancer (both innovations), rheumatic heart disease, ischaemic heart disease (coronary care units) and renal failure. For ages 0-74 the regression shows a good correlation for HIV, breast cancer (both innovations), leukaemia, ischaemic heart disease (coronary care units), cerebrovascular disease (both innovations) and peptic ulcer, thereby confirming HIV, leukaemia and cerebrovascular disease (both innovations) from the previous approach and additionally suggesting breast cancer (both innovations), ischaemic heart disease (coronary care units) and peptic ulcer. Table 6.4 below summarizes all findings from the three approaches and for the two age groups.

Table 6.3 Regression of changes in mortality on timing of innovation for all ages and ages 0-74 (two sexes combined)

		All ages				Ages 0-74			
Condition	**Intervention**	**R^2**	**B**	**p**	**Association?**	**R^2**	**B**	**p**	**Association?**
HIV	**Antiretroviral treatment**	0.090	0.446	**0.000**	**yes**	0.270	0.635	**0.000**	**yes**
Malign. colorectal neoplasm	Colonscopy	0.107	0.513	0.452	no	0.027	0.273	0.590	no
	Oxaliplatin treatment	0.094	-0.504	0.236	no	0.013	-0.202	0.610	no
Malign. neoplasm of cervix uteri	Introduction cervical screening	0.058	0.172	0.580	no	0.055	0.180	0.555	no
Hodgkins disease	High dose therapy and peripheral blood stem cell transplantation	0.001	0.101	0.908	no	0.067	0.359	0.181	no
Malign. Neoplasm of breast	**Mammography**	0.516	0.545	**0.003**	**yes**	0.741	0.320	**0.000**	**yes**
	Tamoxifen	0.544	0.116	**0.002**	**yes**	0.745	0.667	**0.000**	**yes**
Malign. neoplasm of testes	Treatment with cisplatin	0.013	-0.161	0.796	no	0.004	-0.081	0.795	no
Leukaemia	Improved treatment	0.006	0.155	0.766	no	0.480	1.388	**0.000**	**yes**
Rheumatic heart disease	Artificial valve replacement	0.138	0.805	**0.001**	**yes**	0.042	0.444	0.382	no
Hypertension	Increased number of patients treated	0.125	1.322	0.438	no	0.029	0.561	0.594	no
Ischaemic heart disease	B-blockers	0.490	1.499	**0.004**	**yes**	0.023	0.265	0.372	no
	Coronary care units	0.912	1.021	**0.000**	**yes**	0.188	0.492	**0.001**	**yes**
Heart failure	ACE inhibitors	0.039	0.672	0.171	no	0.119	1.605	0.117	no
Cerebrovascular disease	**Treatment of hypertension**	0.235	0.608	**0.016**	**yes**	0.387	0.660	**0.000**	**yes**
	Intensive management	0.888	4.593	**0.000**	**yes**	0.262	0.995	**0.000**	**yes**
Peptic ulcer	Cimetidine	0.001	0.034	0.864	no	0.166	0.620	**0.000**	**yes**
Renal failure	Cyclosporin	0.463	2.394	**0.001**	**yes**	0.030	0.709	0.452	no

Table 6.4: Overview of the evidence for associations between innovations in health care and mortality trends

		All ages			Ages 0-74		
Condition	**Intervention**	**stat.Test**	**Country counts**	**regression**	**stat.Test**	**Country counts**	**regression**
HIV	Antiretroviral treatment	X	X	X	X	X	X
Malign. colorectal neoplasm	Colonscopy		X				
	Oxaliplatin treatment						
Malign. neoplasm of cervix uteri	Introduction cervical screening						
Hodgkins disease	High dose therapy and peripheral blood stem cell transplantation						
Malign. Neoplasm of breast	Mammography			X			X
	Tamoxifen			X			X
Malign. neoplasm of testes	Treatment with cisplatin						
Leukaemia	Improved treatment					X	X
Rheumatic heart disease	Artificial valve replacement			X		X	
Hypertension	Increased number of patients treated					X	
Ischaemic heart disease	B-blockers		X	X			
	Coronary care units			X			X
Heart failure	ACE inhibitors						
Cerebrovascular disease	Treatment of hypertension	X	X	X		X	X
	Intensive management		X	X		X	X
Peptic ulcer	Cimetidine						X
Renal failure	Cyclosporin			X			

6.4 Discussion

This report describes the analytic steps and methods of work package 5 that were applied in order to find associations between specified innovations in health care and changes in mortality trends. The results from different analytical strategies suggest different causes of death as candidates for indicators of amenable mortality (as summarized in Table 6.4). **First**, the statistical test shows that the dates that were identified in WP 2 for the introduction of innovations in health care are only loosely related to changes in the mortality trends. The sensitivity analysis shows that this may partly be related to insufficient data quality of some sources of information. **Second**, applying the number of countries with a match as a criterion we find evidence for HIV, malignant colorectal neoplasm, leukaemia, rheumatic heart disease, hypertension, ischaemic heart disease and cerebrovascular disease, depending on the age range we looked at. Only HIV and CVD were validated in both age ranges. **Third**, the results of the regression analysis show that several innovations show an association with favourable changes in mortality: For all ages combined these were HIV, rheumatic heart disease, IHD, CVD, renal failure and breast cancer. For ages 0-74 we identified HIV, breast cancer (both innovations), leukaemia, ischaemic heart disease (coronary care units), cerebrovascular disease (both innovations) and peptic ulcer. HIV, breast cancer (both innovations), ischaemic heart disease (coronary care units) and cerebrovascular disease (both innovations) were confirmed in both age groups.

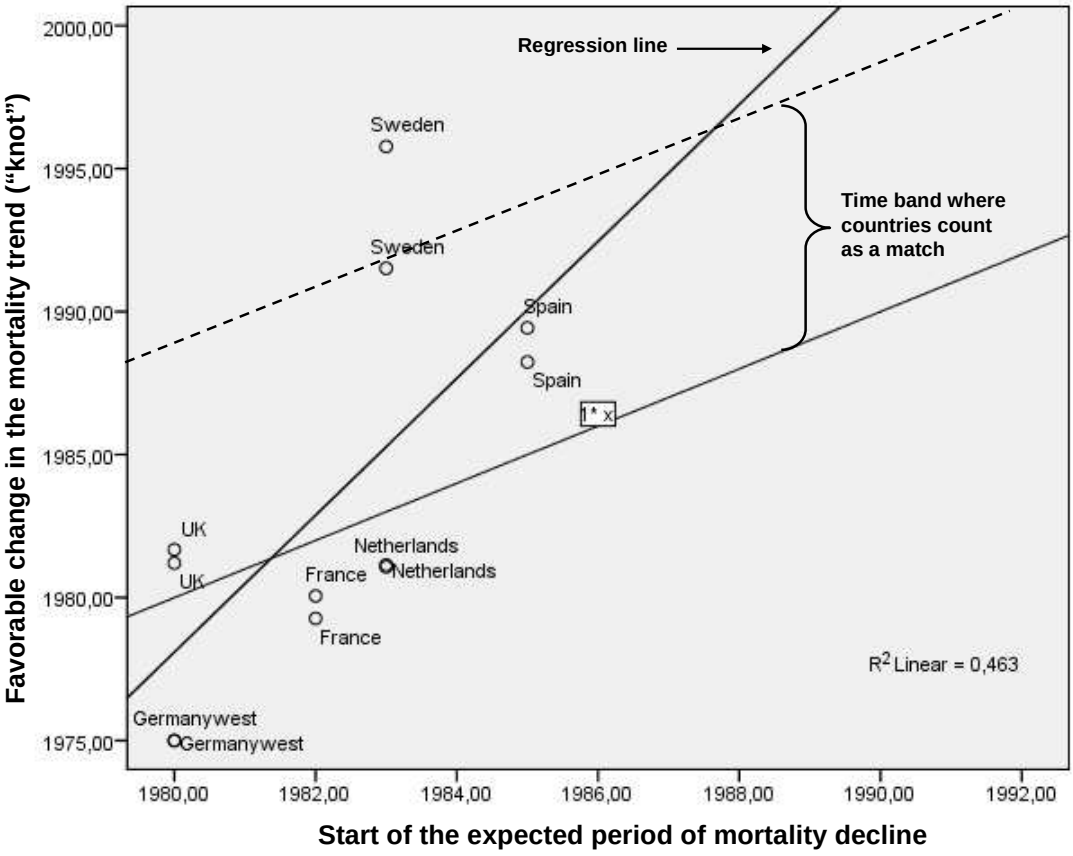
The fact that the slight difference in the age range (including or excluding deaths above age 74) resulted in substantially different lists of amenable mortality indicators may partly be attributed to a real difference in the effectiveness of health care below and above age 75. However, the surprising finding that responsiveness to health is not higher in lower ages also suggests that we have to deal with a critical degree of randomness in determining knots and matches. It was necessary to apply objective quantitative statistical rules to detect knots and matches, but this procedure also selected changes in the mortality trend as being <u>statistically significant</u> that did not turn out to be <u>relevant</u> when looking at the graphs.

Taking into account these unavoidable shortcomings of the procedure, we still think that an automized statistical approach is superior to an arbitrary selection and definition of what is “an important change” based on visual inspection of the graphs. Our expectations on when a mortality decline should have occurred, based on the information from work package 2, can be considered as a hypothesis. In order to perform a rigid hypothesis testing it was important to apply strict rules of whether or not a mortality decline falls within the expected time period or not. For example, by the method of counting these matches per country breast cancer was not confirmed, while looking at the graph of mortality from beast cancer, one could conclude that there was a common factor in several countries in similar years (be it in health care or not). But also the two quantitative methods of (1) counting the matches and (2) regression, we found inconsistent results, two of which should be discussed as examples here:

1. For IHD (coronary care units), the regression shows a clear relationship for both age groups, but in step 2 from above we found only a few matching cases for this innovation. This is due to the fact that,

although countries follow a linear pattern, for many countries the temporal distance between innovation and change in mortality is too large, so they do not match the periods defined in work package 2 because they are outside the predicted period where a change in mortality can be expected. 2. For renal failure we obtain a good fit of the regression model for all ages combined that shows that the later the innovation, the later the mortality improvement. However the regression line has a steeper slope than the one predicted by the expected periods from work package 2 (see Figure 6.33 below). In Figure 6.33 the time band in which a country must lie in order to be counted as a match goes from the line with the function 1*X (lower bound, i.e. we see a change in mortality at the same time as the innovation started) up to the dotted line (upper bound, i.e. we see a change in mortality about 8 years after the innovation). Like this it is possible that the regression shows a good fit, but only a few cases are matching the expected timing (men and women in the UK, men and women in Spain, and men in Sweden), because the empirical linear association is different in its slope from the expected one.

Figure 6.33: Graph of the regression of favourable changes in mortality from renal failure ("knots") on the expected period of mortality decline (based on timing of introduction of Cyklosporin). Mortality changes for both men and women in one country are included, taking into account autocorrelation.



The regression measures a slightly different quality of the results, namely whether or not there is a linear relationship between innovation and times of changes in mortality among all countries. With regards to the exact predictions of when the mortality decline should occur, a regression is more an explorative method than a confirmative one. By counting the number of matches instead, we look more strictly whether the timing of changes in mortality is according to our hypothesis, which is not influenced by the position of the non-matching countries. Thus, linearity of the association is a necessary but not a sufficient quality to confirm the hypothesis. We consider the regression to be an additional valuable approach to assess the overall evidence, but we do not judge the results as superior to the results from simpler methods above, i.e. counts of matches.

To conclude, the present set of analyses represents the core analytic step of the AMIEHS project where evidence from literature reviews (WP 1) and an intensive data collection on innovations in health care (WP 2) were confronted to empirical mortality data from 7 European countries. Our analysis, which is the first attempt to systematically look for associations between amenable mortality on the population level and the timing of innovations in health care, shows that from our initial list of indicators, only a small number of conditions show such association. The results show that only for HIV and cerebrovascular disease an association between innovation in health care and a positive change in mortality could be clearly demonstrated. The results for other conditions (malignant colorectal neoplasm, leukaemia, rheumatic heart disease, hypertension and ischaemic heart disease) differ by methodological approach and age range. We conclude that there is only weak evidence for an association between the introduction of predefined innovations in health care and mortality trends.

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Appendices:

C: 32 international graphs with the periods of expected mortality decline for ages 0-74

D: 192 national graphs (all ages)

E: 193 national graphs (ages 0-74)

7. Identifying candidate indicators of health system performance using the concept of amenable mortality: results of a Delphi exercise (Results of work package 6)

Authors: Bernadette Khoshaba, Marina Karanikolos, Martin McKee
Affiliation: London School of Hygiene and Tropical Medicine, London

7.1 Background

The AMIEHS project has sought to identify putative indicators of health system performance based on the concept of amenable mortality. The concept is simple; premature deaths from certain causes are considered amenable in the presence of timely and effective health care. However, it is more difficult to operationalise it. First, it may be difficult to ascertain the extent to which observed changes in deaths from a particular condition can be attributed to health care. It is necessary to take account of any changes in data recording (such as discontinuities in coding of case of death) and changes in incidence, driven by factors lying beyond the health system. It may also be difficult to obtain empirical evidence of the contribution made by particular innovations in health care, especially as the benefits are often incremental, with progressively better treatments building on each other. Second, measures of the effectiveness of health care have an in-built obsolescence. The most effective health care innovations will reduce death rates to very low levels, so that random variation precludes meaningful comparisons. Thus, while historically, rates of many of the major infectious diseases were excellent indicators of the performance of health systems but are now responsible for only a handful of deaths in many high-income countries. Consequently, while it relatively easy to identify conditions from which death rates are amenable to health care, it is rather more difficult to judge whether they might make useful indicators.

Consequently, for a cause of death to be useful as an indicator of health system performance it will ideally be sufficiently common to generate meaningful numbers, even in small countries. There will be no ambiguity about its definition so that the codes use to record it will be consistent over time and across countries. There will be clear evidence linking it to identifiable health care interventions of known effectiveness, including evidence that the introduction of such interventions can be related in time to declines in mortality. And it will not be subject to marked differences in incidence. In practice, perfection is not possible to achieve so, if causes of death are to be used to assess performance of health systems it is necessary to determine whether they meet these criteria sufficiently to be meaningful. There is no formulaic way of doing so.

Instead, it is necessary to use expert judgement. This can be done in a number of ways, such as the traditional method of assembling a committee of experts. However, committees have many limitations in that they tend to be dominated by individuals and they often lead to important items of information being excluded from consideration. An alternative is voting, which in this case would require individuals to cast votes for the inclusion or exclusion of potential indicators. However, this precludes the exchange of information on why each person reached their decision. A third way is to use one of

the range of consensus processes. These take a number of forms, such as nominal groups or Delphi methods.[1] The precise methods vary but, in many, they involve the posing of an explicit question, the presentation of information for consideration, voting (perhaps with provision to justify why things were voted for or against), feedback to each individual of where they are in the range of votes cast, and a second and final round of voting. There is now considerable evidence that this approach leads to better decisions than the traditional methods. In this document we describe the use of a Delphi process to achieve consensus on indicators of health system performance based on causes of death amenable with timely and effective health care.

7.2 Methods

The first step was to assemble the information required to inform the decision-making process. This began with a systematic search to identify causes of death that had fallen by 30% (selected as a meaningful reduction in mortality) or more between 1979 and 2000, in England and Wales (as this coincided with the period in which ICD-9 was in use). Causes of death from which the number of deaths was fewer than 100 in 2000 were excluded as they would be of little use in comparisons of much smaller countries. For each condition, a systematic review was undertaken to identify evidence from clinical trials and observational studies of the effect of innovations in health care that could plausibly be associated with observed declines in mortality (Box 7.1). The timing of introduction of these innovations was then determined in seven countries and this was compared with trends in mortality from the corresponding causes of death (Box 7.2). In this way it was possible to examine a series of natural experiments.

Box 7.1: Literature reviews

Once we had identified causes of death where there was some suggestion that health care *may* be effective in reducing mortality (either a substantial fall in death rates or improved cancer survival) we sought to identify what specific treatments might be implicated. This was done on the basis of our own clinical knowledge and by consulting standard textbooks. We then systematically sought evidence of the effectiveness of the various interventions in reducing mortality. This was not easy as few RCTs have mortality as an end point, few compare an intervention with placebo, and most are undertaken on a narrow selection of often unrepresentative patients. We also looked for published evaluations of natural experiments, such as those that have looked carefully at mortality at a time when a new treatment was being introduced.

[1] Black N, Murphy M, Lamping D, McKee M, Sanderson C, Askham J, Marteau T. Consensus development methods: a review of best practice in creating clinical guidelines. J Health Serv Res Policy. 1999 Oct;4(4):236-48.

Box 7.2: Identification of changes in mortality trends

For England and Wales, Estonia, France, Germany, the Netherlands, Spain and Sweden cause-specific mortality data describing the period between 1970 and 2005 were gathered by 5-year age categories and gender. Only West-Germany is included in this analysis because we did not have information on the introduction of innovations in health care for East Germany. Within this 35 year period several ICD-coding systems were used. Correction factors were developed to take into account the influence of changes in ICD coding on the mortality trends. No age limit was used for the analysis.

In order to identify changes in the mortality trend Joinpoint models were estimated based on linear spline regression. Three "knots" (significant changes in the mortality trend) were found to be sufficient to describe all the mortality patterns observed, and these split the study period into 4 parts. An age-period-cohort (APC) analysis was also performed but none of the conditions showed cohort effects which confounded the analysis of period changes in the mortality trend.

From all "knots" identifying a change in the mortality trend we only considered points indicating a "favourable change", i.e. an acceleration of mortality decline, a deceleration of mortality increase, or a change from increase to decline. For all these knots we established whether they coincide with the period where an effect on mortality of the introduction of a medical innovation can be expected. This expectation was based on the time of introduction of this innovation in each country, taking into account the time needed for an innovation to be implemented widely and to impact on mortality. If a knot falls within the period in which an effect could be expected this was defined as a "match" between mortality trend and an innovation in health care. The total number of matches found in our analysis is significantly higher than could be expected to occur on the basis of chance alone.

In the vignettes we provide a short summary of the mortality trends in the seven countries between 1970 and 2005 and report the number of countries where we found an association between mortality trends and the introduction of health care innovations.

An expanded list of potential indicators was then created. This included the 14 causes of death that met the criteria of accounting for over 100 deaths per year in 2000 and exhibiting a 30% reduction in death rate between 1979 and 2000 that could plausibly be attributed to particular health care interventions. However, in recognition of the possibility that these criteria might be judged as too strict by those who might use such indicators, it also included a further 12 that did not. These were conditions where: it was not possible to attribute any mortality decline to a particular advance in treatment that had been introduced in the past 30 years; mortality had declined between 1979 and 2000 by between 20 and 30%; there were less than 100 deaths in England and Wales in 2000; and a few conditions added as checks where there was no good evidence that health care would reduce premature deaths (such as lung cancer).

The evidence obtained in this process was then combined into a series of vignettes (appendix F). These included information on trends in incidence, the number of deaths in 2000 in a series of countries of different sizes and from western and central Europe (UK, Netherlands, Spain, and Hungary), the percentage decline in death rate in England and Wales between 1979 and 2000, published evidence on the effectiveness of health care interventions from clinical research (typically randomised controlled trials), published evidence of improvements in outcomes at population level attributed to health care interventions, and observed associations between population level mortality and specific interventions in 7 European countries (United Kingdom, Netherlands, Germany, Estonia, Spain, Sweden, France).

We identified 29 individuals who were either producers or users of evidence on health systems performance, seeking participation by both genders, a range of countries, and health professionals and non-health professionals.

The exercise was completed online, using the Survey Monkey programme. All those who initially agreed to participate completed both rounds. They were asked to score each cause of death on a scale of 1 to 9, where 1 was an entirely inappropriate indicator of health system performance and 9 was an entirely appropriate indicator. For the purposes of the exercise, we made clear that we were interested in conditions where *health systems* prevent death. We used a narrower definition of a health system than that in the 2000 World Health Report. We are interested in interventions delivered by those working in medical care but also those delivered by public health agencies, such as immunisations and screening for cancer. We excluded causes of death which primarily reflect the effectiveness of intersectoral action. In the first round they were also asked to comment on why they allocated the scores they did.

At the end of the first round, the distribution of scores for each cause was recorded and each participant was fed back both the distribution and their personal score, along with a summary of the comments that had been made. They were then asked to rescore them. In keeping with conventional usage, consensus was deemed to exist when, after excluding the highest and lowest individual scores, the remainder lay within a three point range.

7.3 Results

23 individuals agreed to participate and their characteristics are summarised in Table 7.1.

Table 7.1 Details of participants in the Delphi exercise

Countries	1 Australia 1 Canada 2 Denmark 1 Estonia 1 Finland 3 France 1 Italy 1 Lithuania 2 Netherlands 1 New Zealand 1 Poland 1 Portugal 1 Sweden 1 Switzerland 4 United Kingdom 1 United States of America
Gender	17 male; 6 female
*Position	15 university; 4 health ministry; 1 government institute; 5 International; 1 private organisation

* Some of the participants held more than one position

At the end of the first round there was a wide dispersion of scores for almost all causes of death. Details of the distributions of scores in both rounds and for each condition are in the appendix F. By the end of the second round, the distribution had narrowed for 21 out of the 24 causes. However, even after feedback and review of scores, consensus was achieved for only three conditions, neoplasm of the rectum and colon, the cervix, and cerebrovascular disease (Table 7.2). The reasons given for decisions on each condition are summarised in the following paragraphs (for complete comments see appendix F). We first examine the causes on which there was consensus about appropriateness.

Table 7.2 Results of the Delphi exercise

Condition	Consensus achieved	Median score
HIV_AIDS	No	7
Malignant neoplasm of rectum and colon	**Yes**	7
Malignant neoplasm of cervix uteri	**Yes**	7
Malignant neoplasm of the testis	No	6
Hodgkin's disease	No	7
Rheumatic heart disease	No	6
Hypertension	No	7
Ishaemic heart disease	No	7
Heart failure	No	6
Cerebrovascular disease	**Yes**	7
Peptic ulcer	No	6
Renal failure	No	6
Congenital heart disease	No	7
Conditions originating in the perinatal period	No	6
Cancer of the stomach	No	5
primary cancer of the bone	No	4
Leukaemia	No	6
Abdominal hernias	No	7
Suicide	No	3
Cancer of the larynx	No	4
Cancer of the female breast	No	8
Diabetes	No	7
Acute appendicitis	No	7
Cancer of the lung, bronchus and trachea	No	5

Note: A score of 1-3 indicates that the cause is considered inappropriate as an indicator of health system performance, while that from 7-9 indicates that it is appropriate

Malignant neoplasm of rectum and colon was accepted as appropriate, with participants commenting on recent evidence for the effectiveness of screening to detect early disease. However, some questioned what an appropriate upper age limit for “amenability” would be.
Malignant neoplasm of the cervix uteri was also considered appropriate, with screening and immunisation against human papilloma virus identified as effective interventions, although one questioned whether screening should be regarded as falling within health care.
Cerebrovascular disease was also identified as appropriate, although the observed declines in mortality could not be attributed to a single intervention.

Turning to those conditions for which there was no consensus, although treatment for HIV by antiretrovirals has been shown to be effective, there are other contributing factors that need to be considered. These include the changing incidence and in particular the contribution of migration, with many new cases in migrants.

Somewhat surprisingly, the review of evidence did not confirm the temporal association between declining deaths from malignant neoplasm of the testis and the introduction of cisplatin, as the decline began before the drug was available in several countries. Furthermore, the number of deaths is now low. There has also been substantial success in reducing deaths from Hodgkin’s disease but, as with testicular cancer, death rates are now low. Concerns about low death rates, which would particularly affect comparisons using countries with small populations, were expressed with regard to abdominal hernia and peptic ulcer. In seeking to explain trends in heart disease, several participants noted the difficulty of distinguishing the effect of health care from underlying changes in incidence, reflecting among others changes in diet and smoking. Similarly, deaths from suicide were felt to reflect a variety of factors within and outside the health system, in this case with the latter predominating.

Some participants felt that the use of heart failure was problematic because of potential variation in diagnosis and coding, complicated by the frequent co-existence of other conditions. In some cases the ICD codes were considered inadequately precise to capture the complex diversity of conditions of varying degrees of severity and susceptibility to health care. These included congenital heart disease, renal failure, conditions arising in the perinatal period, and leukaemia (although the last could be addressed in part by differentiating deaths at different ages. Finally, for some conditions, such as lung and bone cancer, it was not easy to identify an effective intervention.

7.4 Discussion

The Delphi method is used in circumstances where there is uncertainty and a degree of judgement is required to reach a conclusion. It overcomes many of the known limitations of committees, where a few individuals may dominate the discussions, and ensures that each individual's views are heard. Its two-round structure provides a means by which these different views can be taken into account and, hopefully, a degree of consensus can be achieved.

It cannot, however, create consensus where none exists and, in this case, it was not possible to achieve consensus for all but a few conditions. There was a degree of convergence of scores for all conditions, assessed as an increase in the numbers giving the median score, but this was largely as a result of movement by those who were already close to the median. There was little change in those who took an outlying view from the beginning. It was clear from the comments provided by participants that the process of deciding was extremely difficult. This was despite, or perhaps because of, the strenuous efforts to bring together as much of the relevant information, going far beyond what had ever been done before for conditions potentially amenable to health care. Each individual was required to assess, weight, and combine information according to many different criteria. Inevitably, their decisions would be shaped by the weighting they placed on these criteria. This was most apparent with those who gave outlying scores. Thus, it was clear that some placed a proportionately greater weight on the scope to prevent certain conditions from arising than did others. Others, especially those from small countries, were especially concerned about the instability arising from the small numbers of deaths from certain causes (a reflection of past successes of health care). There were also divergent views about the scope of health care, such as whether the health system can be held accountable for differences in policies on screening, or what its role should be in improving uptake of interventions known to be effective.

What does this imply for the use of the conditions considered to assess the quality of health care? It reinforces a view that has emerged in the course of the project that the interpretation of data on amenable mortality is complex. Simple rankings can be misleading. They can only be a starting point for a more detailed enquiry. The comments provided by the participants illustrate the issues that must be taken into account. They include changes in the occurrence of a condition in a given country, either because of an increased incidence or, as in the case of AIDS, a change in the population at risk as a consequence of migration. They also include the number of deaths, a problem that applies particularly to small countries. However, given the clear evidence that health care has made a difference to mortality from many of the conditions studied, even if it is not possible to quantify the impact of the introduction of individual interventions, it should not be interpreted as meaning that the concept should be discarded. An example is breast cancer. There is little doubt that the remarkable reductions in mortality in recent years in some countries Rather, it should be used with caution and, especially, based on a detailed understanding of the many potential factors, of which health care is one, that are driving changes in death rates.

Acknowledgements: We are very grateful to the participants who gave up their time to complete this exercise

8. Preparation of an electronic atlas of amenable mortality (Results of work package 7)

Authors: Iris Plug, Rasmus Hoffmann, Frank Santegoeds, Johan Mackenbach
Affiliation: Erasmus MC, Rotterdam, The Netherlands

8.1 Introduction

In the AMIEHS project we aimed at the development of a new list of indicators for amenable mortality. After an extensive selection procedure the appropriateness of the indicators was judged through a Delphi exercise. Finally the project is concluded with an illustration of the results. This is done through the construction of an electronic atlas that can be accessed through the web.

The atlas resulting from the AMIEHS project is the third European Atlas of "Amenable Death". The first European community Atlas of "avoidable death" was published in 1988 as a result of the EC Concerted Action Project on Health services and "Avoidable Deaths"[1-2]. This major work has been updated twice. The first edition and the first volume of the second edition each cover 17 disease groups in 10 countries, which were considered to be effectively treatable or preventable by health care services. Health care services were interpreted as to include primary care, hospital care and community health services such as screening and public health programs. The second edition describes "avoidable mortality" in the European Community in 1980-1984 and changes in "avoidable mortality" between 1974-1978 and 1980-1984 in two volumes. Following this tradition other country and region specific (e.g. Australia and New Zealand) atlases describing area specific information on levels of avoidable mortality have been published[3].

The main objective of work package (WP 7) in which the electronic atlas is constructed was to illustrate the use of amenable mortality indicators by preparing an e-atlas of variations in amenable mortality. The focus is on conditions that are amenable by health care innovations introduced after 1970. The new atlas describes the time period between 2001 and 2009 for 40 causes of death in 30 European Countries.

8.2 Methods

Data

Mortality data were obtained for 30 European countries (EU member states, applicant countries and EFTA countries) and 24 causes of death (+ 21 extra causes). A complete dataset was provided by EuroStat (http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home). The selection of causes of death consists of the causes of death that were presented to the Delphi panel and causes of death used in previous lists of amenable mortality (n=16). The latter are added to provide extra information for the user on mortality trends of causes of death that have been used as indicators of

amenable mortality in previous studies. Because of availability of data this can only be done if the specific cause of death was part of the European shortlist of Causes of death, published by Eurostat, which means that mortality data can be accessed by the public.

Analyses

Mortality data were specified by 5-year age groups, sex and cause of death describing the time period between 2001 and 2009. However for many countries data on 2009 are not available yet. Age standardized mortality rates were calculated using a direct standardization method and applying the European standard population. Mortality rates in different age categories are compared using 5 age groups, namely 0-14 yrs, 15-29 yrs, 30-59 yrs, 60-74 yrs and 75+. Confidence intervals were calculated using a Poisson distribution.

Atlas

An electronic atlas was created using the data presentation software package InstantAtlas software which was provided by ESRI. The atlas is available on the project website, but also on the website of the Department of Public Health of the Erasmus MC.

Per cause of death mortality trends are shown for males and females separately presenting age standardized mortality rates per year over a time period between 2001 and 2009 and for each cause of death trends in five age categories are presented. Histograms incorporating 95% confidence intervals are used to compare age standardized mortality rates and to get insight in the distribution. The software package enables the comparison of time trends in European countries. The output is an interactive dynamic report.

8.3 Results

In the electronic atlas trend data are shown on 45 causes of death in 30 European countries. The studied conditions can be divided into 3 groups, conditions selected in work package 1 (Table 8.1a), conditions that did not meet all selection criteria but used as input in the Delphi procedure (Table 8.1b) and conditions that have been defined as “amenable” in earlier studies on amenable mortality (Table 8.1c). In the final atlas all conditions are presented in order of ICD 10 coding. Information on availability of mortality data within the presented countries can be found in appendix A.

Table 8.1a. Group A conditions (n=16): conditions that have been selected in WP1

Cause of death	ICD 9 code	ICD 10 code
HIV	042-044	B20-B24
Malignant colorectal neoplasm	153,154	C18-C21
Cancer of the female breast	174	C50
Malignant neoplasm of cervix uteri	180	C53
Malignant neoplasm of testes	186	C62
Hodgkin's disease	201	C81
Lymphocytic leukemia	204-205	C91
Rheumatic heart disease	390-398	I00-I09
Hypertension	401-404	I10-I13
Ischaemic heart disease	410-414	I20-I25
Heart failure	428-429	I50-I51
Cerebrovascular disease	430-438	I60-I69
Peptic ulcer	531, 532	K25-K26
Renal failure	584, 585, 586	N17-N19
Congenital heart disease	745-746	Q20-Q24
Conditions originating in the perinatal period	760-779	P00-P96

Table 8.1b. Group B conditions (n=8): conditions that did not meet the selection criteria but used in Delphi procedure

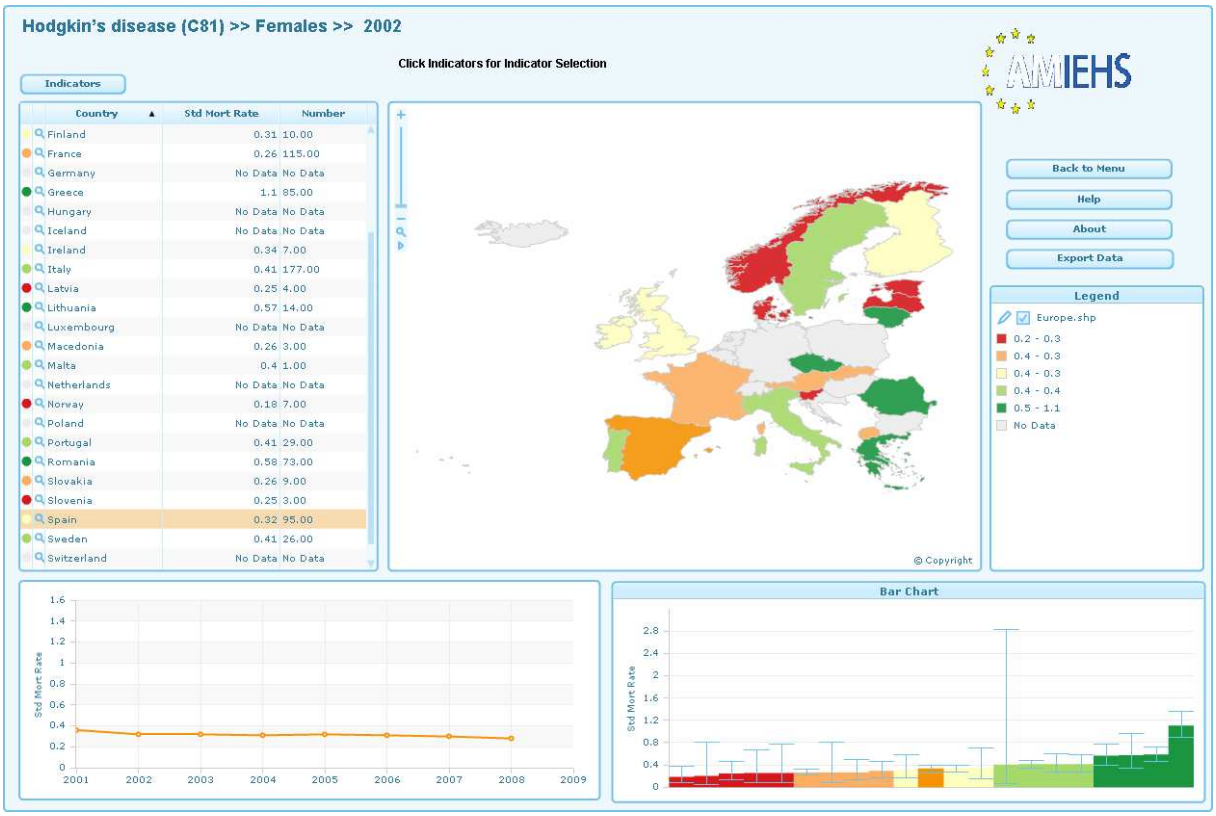
Cause of death	ICD 9 code	ICD 10 code
Cancer of the stomach	151	C16
Cancer of the larynx	161	C32
Cancer of the lung, bronchus and trachea	162	C33-C34
Primary cancer of bone	170	C40-C41
Diabetes	250	E10-E14
Acute appendicitis	540	K35
Abdominal hernias	550-553	K40-K46
Suicide	E950-E958	X60-X84

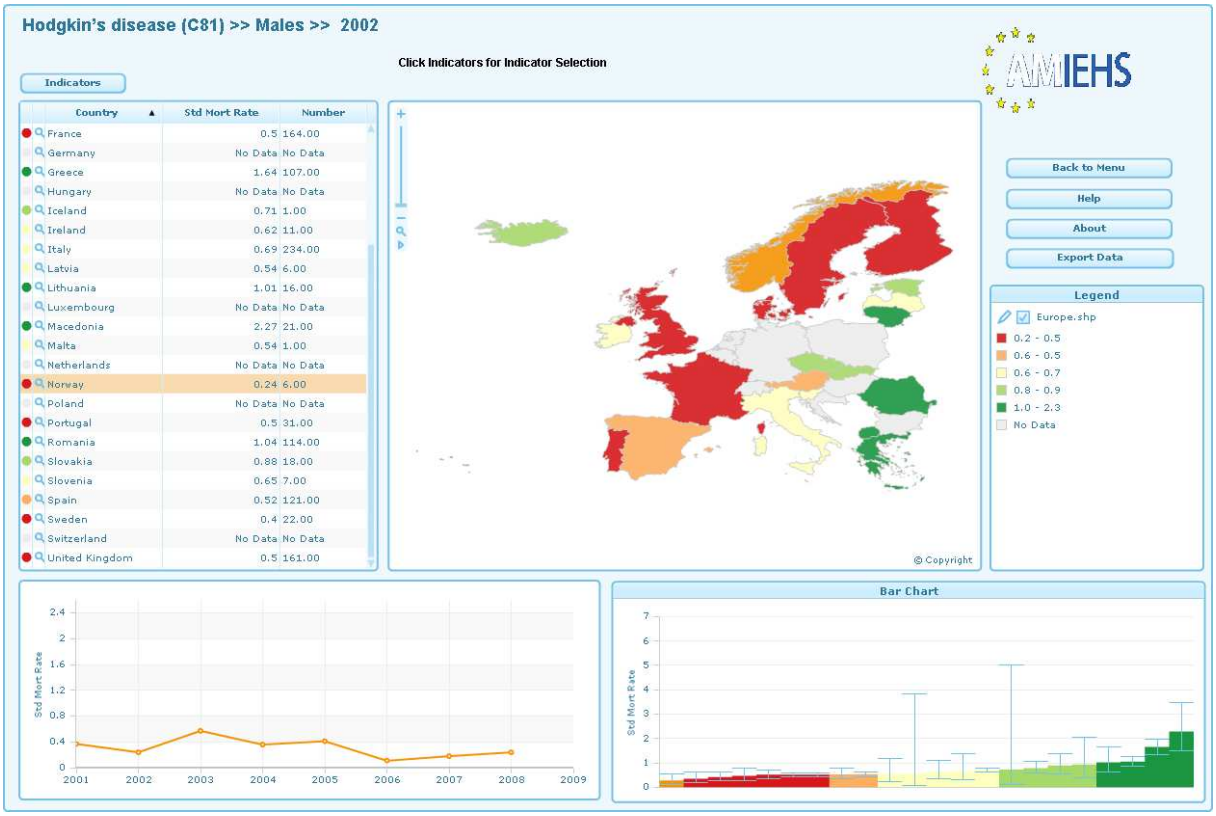
Table 8.1c. Group C conditions (n=21): conditions defined as "amenable" in earlier studies and presented on European shortlist of Causes of death

Cause of death	ICD 9 code	ICD 10 code
Respiratory Tuberculosis	10-11-12	A15-A16, J65
Meningococcal infection	036	A39
Bronchitis and pneumonia	466,480-486	A48.1,J12-J18
Hepatitis	070	B15-B19
Neoplasm of the liver	155	C22
Neoplasm other skin and lip	172,173	C43,C44
Cancer of the body of the uterus	182	C54
Neoplasm of the kidney	189	C64
Neoplasm of the bladder	188	C67
Aplastic anaemia	284	D60-61
Bacterial meningitis	320	G00
Parkinson's disease	332.0	G20
Multiple sclerosis	340	G35
Influenza	487	J10-J11
Chronic bronchitis, emphysema and chronic airways obstruction, not elsewhere classified	491-492, 496	J41-J44
Asthma	493	J45-J46
Intestinal obstruction with no mention of hernia	560	K56
Complications of pregnancy, childbirth & puerperium	630-679	O00-O99
Congenital anomalies	740-759	Q00-Q99
Falls	E880-E888	W00-W19
Sudden infant death	798	R95

Trends in amenable mortality

As an example of the output of the electronic atlas we present in this chapter pictures of mortality from Hodgkin's disease in males and females in 2002. The pictures for Hodgkin's disease show that for males in 2002 mortality from Hodgkin's disease was high in Spain (0.52 per 100.000) and the low was Norway (0.24 per 100.000). The trend pictures show that in Spain the mortality level was rather constant, while in Norway there were some fluctuations. A link to the complete atlas can be found on the AMIEHS website.





8.4 Discussion

In this international electronic atlas of amenable mortality the trends in mortality are shown for 45 causes of death. This concerns not only causes of death that were selected in AMIEHS, but also causes that have been studied in previous lists of amenable mortality. The reason for expending the list of causes of death is to provide our readers with a broad overview in trends in mortality from causes of death that are possible indicators. Although interpretation should be done with care using knowledge on other disease characteristics like incidence and case fatality, the presented results can offer insight in quality of care in individual countries, but also in Europe over a large diversity of diseases.

We would like to thank Eurostat that have provided us with mortality data for the period 2001-2009.

References

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9. Overall conclusions

In order to identify causes of death which are amenable to health care intervention, and which can be used in routine surveillance systems to identify possible shortcomings in health care delivery, we applied a unique and scientifically rigorous approach. This involved strict selection criteria which were consecutively applied in a series of analyses: mortality has declined in the period 1979-2000; the number of deaths in 2000 is sufficient for meaningful between-country analysis; a specific intervention has been introduced in 1970-2000 which in evaluation studies was shown to be effective; national introduction of this intervention coincided with a favourable change in the national mortality trend.

Following this approach, we were unable to derive a set of amenable mortality-based indicators of the effectiveness of health systems which can be used in routine surveillance systems. Only four conditions fulfilled all the criteria, and only two of these conditions were also agreed on by our expert panel. Yet, even for this limited number of conditions our analysis raises doubts about their validity as indicators of health care effectiveness in between-country comparisons: the trend analysis suggested that other factors contribute to their current mortality rates.

These seemingly ‘negative’ results must, however, be interpreted with caution. The analysis had a number of important and largely inevitable limitations:

- The analysis relied heavily on the availability of scientific evidence on the effectiveness of health care interventions, and on information regarding their time of national introduction. In both cases evidence was lacking or inadequate, as noted above.
- Our study focused on innovations after 1970, because we assumed that health care interventions introduced before 1970 are unlikely now to vary in their implementation between countries. This assumption may be incorrect.

The experience of undertaking this project has forced us to reconsider the approach taken, as well as how we should view the concept of amenable mortality. We remain convinced, on the basis of the totality of the evidence, that improvements in health care have been associated with substantial declines in deaths from many conditions. However, while we focused on the timing of innovations, that is only one factor that must be considered. The others are the coverage of the population by those interventions, as well as the quality with which they are applied. Both take time to develop. For example, we found evidence of how, even now, many European citizens are inadequately treated for hypertension, even though the necessary drugs have been discovered decades ago. Similarly, although the treatment for many acute surgical emergencies has been known for decades, mortality has continued to decline, presumably reflecting a combination of increasing skill in providing treatment and a range of non-specific factors such as safer anaesthesia and better detection and treatment of complications.

Because of these limitations, ‘absence of evidence’ of the effectiveness of health care in reducing population-level mortality does not imply ‘evidence of absence’. It is very likely that some of the between-

country variations in mortality from the conditions we studied do reflect variations in health care effectiveness but it is not possible to link them to specific interventions.

Our study had a number of positive results. First of all, for a number of conditions we found evidence that national mortality trends partly reflect the mortality-lowering effect of health care innovations. This applies to cerebrovascular disease, ischemic heart disease, HIV/AIDS, and colorectal cancer. Although mortality rates from these conditions are likely to reflect several factors, mortality trends have clearly been sensitive to improvements in health care effectiveness.
Secondly, our study suggests that a few conditions which have so far not been included may be added to the list (namely, HIV and colorectal cancer). Our study also confirms that an age-limit of 65 years is not appropriate. We found considerable declines of mortality matched to health care innovations at all ages, and while the number of matches is slightly lower if the analysis is restricted to those dying before the age of 75, there is no reason to restrict the analysis even further.

Thirdly, we were able to make some methodological advances whose value extends beyond amenable mortality. We developed an automated method for detecting disrupted mortality trends due to coding changes, which can be applied in the analysis of cause-specific mortality trends. We also developed a systematic method for relating national changes in health determinants to national changes in mortality, which can be used for many other health determinants than health care effectiveness alone.

Our main recommendations for policy makers are:
- Rates of mortality from amenable conditions are likely to reflect the influence of many different factors, which in at least some cases also include health care effectiveness. This implies that they must be interpreted with caution, and do not without further analysis permit judgements on the effectiveness of health care systems. Instead, they identify the need for further analysis, including disaggregation of data by age, social group and region, and coupling with other evidence specific to the causes being examined such as incidence and case fatality and quantity and quality of health care utilisation, where this exists.
- Commission further research to assess the practical issues that arise when using trends in mortality from conditions amenable to health care intervention as indicators of (changes in) health care effectiveness. In recent years, many new international data on incidence and case fatality of diseases and on health care interventions have become available. Research should assess whether between-country variations in trends of mortality from these conditions reflect variations in health care delivery and examine whether further indicators can be created.

Our main recommendations for researchers are:
- Using data from the period 1990-2010, compare national trends in mortality from a range of amenable conditions with new available data on trends in incidence and case fatality. This analysis may take the concept of amenable mortality to the next stage by taking account of changing patterns of disease incidence.
- For a selection of amenable conditions, carry out in-depth studies of the proportion of deaths and survivors in whom health care quality conforms to the best available evidence of effectiveness, and assess whether

countries with slower declines in mortality from amenable conditions provide care that is less innovative, of lesser quality or with lower coverage.

- For a selection of amenable conditions, carry out in-depth studies of regional and socioeconomic variation in mortality decline, compare mortality trends with trends in health care utilization, and assess whether differences found can be explained by differences in health care.
- For a selection of amenable conditions, carry out in-depth studies of the association between mortality decline and health systems factors known to promote health care quality, such as universal access, role of primary care, funding levels, and implementation of professional guidelines.