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The timing of introduction of pharmaceutical innovations in seven European countries

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Abstract

Rationale, aims and objectives Differences in the performance of medical care may be due to variation in the introduction and diffusion of medical innovations. The objective of this paper is to compare seven European countries (United Kingdom, the Netherlands, West Germany, France, Spain, Estonia and Sweden) with regard to the year of introduction of six specific pharmaceutical innovations (antiretroviral drugs, cimetidine, tamoxifen, cisplatin, oxalaplatin and cyclosporin) that may have had important population health impacts.

Methods We collected information on introduction and further diffusion of drugs using searches in the national and international literature, and questionnaires to national informants. We combined various sources of information, both official years of registration and other indicators of introduction (clinical trials, guidelines, evaluation reports, sales statistics).

Results and conclusions The total length of the period between first and last introduction varied between 8 years for antiretroviral drugs and 22 years for cisplatin. Introduction in Estonia was generally delayed until the 1990s. The average time lags were smallest in France (2.2 years), United Kingdom (2.8 years) and the Netherlands (3.5 years). Similar rank orders were seen for year of registration suggesting that introduction lags are not only explained by differences in the process of registration. We discuss possible reasons for these between-country differences and implications for the evaluation of medical care.

Introduction

The introduction and diffusion of innovative drugs

Key goals of health systems are to improve the health of the population and to do so in an equitable way [1]. Although the health of the population to a large extent is influenced by broader improvements in living conditions [2], well-functioning health care systems also contribute to the health of populations. However, their ability to do so varies and there is increasing interest in measuring their performance; the introduction and diffusion of medical innovations should be an important part of this process.

There have long been concerns about the delay in introducing innovative drugs in different countries [3,4]. These have drawn on analyses of variations in the year of registration between countries. For instance, this has been reported to have been somewhat delayed in the United States, Sweden and Italy when compared with United Kingdom, West Germany and France [3,4]. However, given the relative ease in obtaining data on year of registration, delays in the registration process have been the main focus of debate about international variation in the timing of introduction of innovative drugs [5,6] even though other health system factors have also been identified [7,8].

In the European Union (EU), there has been a process of harmonizing the regulation of new drugs [9]. However, for a drug to impact on the health of the population, it must also be used in clinical practice. This will often not coincide with registration decisions. For instance, pharmaceuticals may have been used in clinical trials before registration year (which may have a

considerable impact if trials are relatively large and the condition is rare), or there may have been a delay after the registration year before the drug is widely adopted.

The theory of diffusion [10] of innovations envisages cumulative adoption following an S-shaped curve, with Rogers describing diffusion of innovations as 'the process through which an innovation is communicated through certain channels over time among the members of a social system' [11]. The adaptors of the innovation are classified into five different categories. (1) Innovators, about 2.5% of the 'population'. They are not opinion leaders, but prone to novelty and with little to lose. (2) Early adopters include opinion leaders that interact with innovators and like-minded persons. Thereafter come: (3) early majority, who tend to rely heavily on the early adopters and (4) the late majority, which relies in turn on the early majority. They are considered more conservative and will not adopt an innovation until it is standard practice. Finally, (5) the 'laggards', (or traditionalists), wedded to the 'old ways', are critical of new ideas and will only accept them once the new idea has become mainstream or even tradition.

There are several published empirical studies on diffusion of innovation. Commonly, these are descriptive studies showing the variation in the time of introduction of new innovations. Other studies analyse 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 [12–15] as well as gender, age and social differences [16,17]. Most studies analyse diffusion within a specified country but some make international comparisons [18–21]. These studies have used a variety of empirical data such as health administrative data [14,22], medical records or questionnaires to or interviews with key informants [23–25]. For pharmaceuticals, official data on registration as well as sales and prescribing statistics of pharmaceuticals [19,20,26] have been used.

Applying the theory of diffusion to the introduction of new pharmaceuticals implies the need to obtain empirical data showing when the innovators and early adaptors started to use the new treatment. However, where our goal is to identify when an innovation might be expected to improve the health of the population, we will need data also on the diffusion of the innovation.

Development of indicators of the effectiveness of health systems

This study is part of the Amiehs project (Avoidable mortality in the European Union: Towards better indicators for the effectiveness of health systems) [27], which seeks to develop indicators of the effectiveness of health systems. Mortality for specific causes of death that are considered amenable to medical care is increasingly used as an indicator of the quality of health care [28]. High death rates from these causes, collectively termed avoidable or amenable mortality, have been suggested to motivate further investigations of the quality of health care. There is now extensive experience in their use in different countries, health administrative areas, socioeconomic and ethnic groups and with respect to gender [29,30].

Several studies have shown that mortality from these causes have decreased more rapidly than total mortality in several industrialized countries [30–32]. For some avoidable causes of death, mortality has also been found to decline faster after the introduction of innovations in health care, such as improved management of hypertension, leading to lower mortality from cerebrovascular disease and screening to prevent deaths from cervical cancer [33]. However, to assess the effectiveness of health care at a population level, a precise measure of the timing of the introduction of innovations is necessary in order to evaluate whether they have impacted on the health of the population.

The objective of this paper is to analyse the variation in the introduction of specific pharmaceutical innovations that may influence the mortality outcome among seven European countries – for comparison – applying both official registration data and indicators of the start of the diffusion of the innovative drugs.

Material and methods

Six pharmaceutical innovations were included in the study (Table 1). These were selected on the basis of their effectiveness, as demonstrated in clinical trials, in reducing specific causes of death, where those causes were sufficiently common and where there had been an observed decline in mortality in recent decades, making it possible to undertake robust statistical testing for any association in another part of the project.

Cisplatin was introduced for the treatment of testicular cancer already in the 1970s and has been shown to improve outcome when included in combination therapy [34]. The H2-receptor antagonist cimetidine was evaluated in clinical trials of peptic ulcer treatment in the late 1970s supporting evidence on the ulcer healing [35,36]. Tamoxifen has been shown to reduce recurrences and mortality from breast cancer in several clinical trials [37]. Cyclosporin is an effective immunosuppressant used in renal transplantation [38]. Clinical trials have found oxalaplatin to be effective as a component of combination therapy for advanced colorectal cancer [39,40]. The antiretroviral drugs azidothymidine and zidovudine were shown to improve survival with AIDS in randomized clinical trials [41]

For these specific innovations, a questionnaire was developed and answered by the participating partners from the United Kingdom, the Netherlands, Germany (West Germany), France, Spain, Estonia and Sweden. The partners collected data from official sources and from key informants. Information was sought on the first introduction of the innovation and the period of implementation. For the first part, documents on the official and organized introduction were asked for. These were for instance, the registration year for pharmaceuticals as well as the year of national

Table 1 Interventions included in the analysis of timing of innovations

Target disease	Medical innovation
Testicular cancer	Treatment with cisplatin
Peptic ulcer	Treatment with cimetidine
Breast cancer	Treatment with tamoxifen
Acute nephritis and nephrosis	Immunosuppressive treatment with cyklosporin for kidney transplantation
Colorectal cancer	Treatment with oxalaplatin
HIV	Treatment with antiretroviral drugs (azidothymidine or zidovudine)

programs and guidelines. 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 was used to verify that the medicine has been available in the respective country and also to indicate the speed of the implementation. To facilitate comparisons between countries, statistics on daily defined doses (DDD) [42] were asked for.

Sales statistics were available from Sweden (1977–2008; only from year of registration), Estonia (1999–2008), Germany (1999–2008; hospital prescribing and privately insured patients were unavailable)) France (2002–2007), United Kingdom (mainly 1999; hospital prescribing unavailable) and Spain (2000–2008; hospital prescribing unavailable). The measure used differed between countries and pharmaceuticals. Sales statistics measured by DDD was available for most of the period from Sweden, Estonia and Germany only.

In addition, 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 and used specific criteria for defining the start of the diffusion:

Criteria 1: The first documented year of introduction of the pharmaceutical in a specific country was used to define the year of the start of diffusion. The start of first clinical trials or clinical studies, available sales statistics from the introduction period or evaluation reports describing the introduction of the pharmaceuticals were accepted as data on the start of the diffusion. If the starting year of the clinical trial was not mentioned, we used the year 3 years before the publication year as the indicator of the introduction. When no data was available, the year of registration was used.

Criteria 2: In order to define the start of the diffusion, we also judged that data indicating a continued diffusion of the drug was needed. This was indicated by further clinical trials, evaluation reports, guidelines and sales statistics.

Thus, several data was used for each statement of the year of introduction. We present in this article the references to the early indicators of the start of diffusion and to evaluation reports and guidelines indicating the further diffusion of the pharmaceuticals. The availability of sales statistics was presented above. When data was available, we analysed the year when the peak level of sales of the pharmaceutical occurred and the diffusion time from start of diffusion to this year. Further references are available in the Amiehs report [27] on the Internet.

The variation in year of introduction among the countries was studied using both official data of year of registration and data on the start of the diffusion of the pharmaceuticals, respectively. The time lag between the first introduction in any of the countries and in the others was calculated. A mean score of the time lag including data on all the six pharmaceuticals was analysed for each country.

Results

With the exception of Estonia, cisplatin was introduced for the treatment of testicular cancer in all countries in the 1970s or early 1980s (Table 2). In Estonia, it was delayed until the 1990s, when the country had achieved independence. In most countries, the introduction started with clinical trials or other clinical studies in the period 1976–1981 [43–47], while registration was some years later, that is, between 1979 and 1983. In several countries, cisplatin was registered for the treatment of cancers at several other sites so sales data could not be used to evaluate its diffusion as a treatment for testicular cancer. One study from the Netherlands found that cisplatin was not in widespread use between 1970 and 1978 [48] (Table 3). In the United Kingdom, The UK Children's Cancer Study Group [49,50] followed up children with testicular cancer from 1979 to 1988, during which period only about 7 % of patients received the drug.

Cimetidine was introduced for the treatment of peptic ulcer in most countries in the late 1970s or early 1980s. In Estonia however, the drug was first registered in 1993. In Germany [51] and France [52,53], clinical trials started a few years before the year of registration. In Spain, the year of registration and first clinical trial coincided [54]

Tamoxifen, used to treat breast cancer, was introduced in most countries in the late 1970s or early 1980s. However, in Estonia, it was first available in the 1990s, where it was registered in 1992. In Germany, clinical trials [12] were reported a few years before registration, and in Sweden, the first reported clinical trials [55,56] coincided with registration.

Immunosuppressive treatment with cyclosporine following kidney transplantation was introduced in the 1980s in most countries with the exception of Estonia where it was again delayed until the 1990s. In most countries, the year of registration and the start of the clinical trials were close in time. However, In Germany, clinical trials were reported 11 years before the official registration. Clinical trials were reported from United Kingdom [57,58], the Netherlands [58], Germany [57], Spain [59] and Sweden [60]. As with cisplatin, interpretation of sales data was complicated by its other indications.

Clinical trials of oxalaplatin started before registration (which was usually at the end of the 1990s) in several countries. The time lag varied between 4 years in the United Kingdom [61] and Spain [62] to 8 years in France [63]. In some countries, the diffusion process can be assessed by consensus statements and guidelines. In the United Kingdom, guidelines were published in 2002, 7 years after the introduction [64] Oxalaplatin was recommended for patients with inoperable liver metastases to make them eligible for surgery [65]. In Germany, a 2000 consensus statement on treatment of colon cancer [66] mentioned oxalaplatin as a promising new drug but not yet generally recommended. In Sweden [67], oxalaplatin was recommended as one alternative in an evidence review from 2001, that is, 13 years after the introduction [68].

The antiretroviral drugs azidothymine or zidovudine were introduced in most countries between 1987 and 1995. In the Netherlands, the registration year coincided with the first reported clinical trial starting in 1987 [69]. In the United Kingdom [70,71],

Table 2 The year of the introduction of medical innovations measured by indications of the start of diffusion of innovations compared to the registration year for selected causes of death

	United Kingdom		The Netherlands		Germany		France		Spain		Estonia		Sweden	
Innovation	DOI	Reg.	DOI	Reg.	DOI	Reg.	DOI	Reg.	DOI	Reg.	DOI	Reg.	DOI	Reg.
Treatment of testicular cancer with cisplatin	1976 [43]	1981	1976 [44]	1982	1973 [45]	1979	1977 [46]	n.d.	1981	1981	1995	1995	1981 [47]	1983
Treatment of peptic ulcer with cimetidine	1981	1981	1977	1977	1979 [51]	1981	1976 [52,53]	1978	1977 [54]	1977	1993	1993	1978 [67]	1978
Treatment of breast cancer with tamoxifen	1976 [85]	1973	1981 [86]	1975	1981	1983	1981	1977	1988 [87]	1977	1992	1992	1976 [55,56]	1976
Immunosuppressive treatment with cyklosporin for kidney transplantation of patients with acute nephritis and nephrosis	1980 [57]	1983	1983 [58]	1983	1980 [57]	1991	1982	n.d.	1985 [59]	1986	1993	1993	1983 [60]	1985
Treatment of colorectal cancer with oxaliplatin	1995 [61]	1999	1999	1999	2001	2001	1988 [63]	1996	1994 [62]	1999	1999	1999	1999	1999
Treatment of HIV with the anti-retroviral drugs (azidothymidine or zidovudine)	1989 [70,71]	1987	1987 [69]	1987	1988 [72]	1987	1989 [73]	1987	1993 [74]	1987	1995	1995	1988(75)	1987

DOI, indication of the start of the diffusion of innovation; n.d., no data available; Reg., based on official data of registration.

Germany [72], France [73], Spain [74] and Sweden [75], clinical trials started a few years after the year of registration. The continued implementation of treatment was verified by sales statistics in all countries. Their use was endorsed by clinical guidelines or recommendations in United Kingdom [76], Germany [2], Spain [77] and Sweden [6]. The guidelines were published between 7 and 17 years after the introduction in the respective country.

As illustrated in Table 4, the variation among countries in the introduction of new drugs was largest for cisplatin, cimetidine and tamoxifen, all introduced first in the 1970s. For the most recent pharmaceuticals, the antiretroviral drugs and oxalaplatin, the variation was considerably less. Some countries were consistently among the first to introduce new drugs, such as Germany, France, Sweden, United Kingdom and the Netherlands. Introduction of modern drugs was delayed until after independence in Estonia, while Spain often introduced the drugs studied later than other countries.

The delay since the first introduction was shortest for France, the Netherlands and United Kingdom (Table 5), and longest for Estonia. This was true both when the official year of registration and when other data on the start of the diffusion of innovation were used. When the start of diffusion was used the variation was greater and the ranking between the countries differed somewhat from what was found using the registration year. For instance, the delay in registration was shortest in the Netherlands (1.3 years) while the time lag until the start of diffusion was shortest in France (2.2 years).

For several innovations, the length of period of diffusion from introduction to the year when the peak level of use was reached was similar (Table 6). This was the case for treatment with cimetidine, oxalaplatin and cyclosporine. For some pharmaceuticals – cisplatin, cimetidine and cyclosporine – a delay in peak level was found in Estonia although when the time length for diffusion was similar. In these cases, the pharmaceuticals were also introduced later in Estonia. Also for tamoxifen, the diffusion started later in Estonia, but this seems however to have been compensated by a faster diffusion (11 years compared with about 20 years in the compared countries). For treatment with cisplatin, the early introduction in Sweden was followed by a fast diffusion, which increased the variation among the countries further. For zidovudine, the diffusion seems to have been fast since the sales of the pharmaceutical peaked before or at the start of the period of available sales statistics in most countries, that is, around the late 1990s.

Discussion

Between-country variation in introduction of pharmaceuticals

Several pharmaceuticals developed in the 1970s and 1980s were introduced about the same time in most countries with the exception for Estonia, where cimetidine, cisplatin and cyclosporine were only introduced in the 1990s. This was true also for treatment of breast cancer with Tamoxifen, although the variation was fairly large also among the other countries. For the drugs developed later, oxalaplatin and antiretroviral drugs, however, introduction was at about the same time in all countries, in the late 1980s or early 1990s.

Table 3 Guidelines and evaluation reports indicating the continued diffusion of medical innovations

Innovation	Country	Documentation	Year
Treatment of testicular cancer with cisplatin	United Kingdom	Evaluation report	1989 [49]
	The Netherlands	Evaluation report	1991 [88]
Treatment of peptic ulcer with cimetidine	The Netherlands	Evaluation report	1983 [89]
Treatment of breast cancer with tamoxifen			
Treatment of colorectal cancer with oxaliplatin	United Kingdom	Guidelines	2002 [64]
	Germany	Guidelines	2000 [66]
	Sweden	Guidelines	2001 [68]
Immunosuppressive treatment with cyclosporine for kidney transplantation of patients with acute nephritis and nephritis	United Kingdom	Evaluation report	1990 [90]
	The Netherlands	Evaluation report	1987 [91]
	France	Evaluation report	1987 [92]
	Spain	Evaluation report	1986 [93]
	Sweden	Evaluation report	1991 [94]
Treatment of HIV with the antiretroviral drugs (azidothymidine or zidovudine)	United Kingdom	Guidelines	1997 [76]
	Germany	Guidelines	2004 [95]
	Spain	Guidelines	2000 [77]
	Sweden	Guidelines	2005 [96]
	Sweden	Evaluation report	1999 [97]

Table 4 Variation in the start of diffusion of medical innovations among countries based on country-specific year of introduction

Diffusion year	Cisplatin	Cimetidine	Tamoxifen	Cyklosporin	Oxalaplatin	Antiretroviral
0	Germany 1973	France 1976	Sweden, UK 1976	Germany, UK 1980	France 1988	The Netherlands 1987
1		Spain, the Netherlands 1977				Sweden, Germany 1988
2		Sweden 1978		France 1982		France, UK 1989
3	The Netherlands, UK 1976	Germany 1979		Sweden, the Netherlands 1983		
4	France 1977					
5		UK 1981	The Netherlands, France, Germany 1981	Spain 1985		
6					Spain 1994	Spain 1993
7					UK 1995	
8	Sweden, Spain 1981					Estonia 1995
9						
10						
11					The Netherlands, Sweden, Estonia 1999	
12			Spain 1988			
13				Estonia 1993	Germany 2001	
14						
15						
16			Estonia 1992			
17		Estonia 1993				
18						
19						
20						
21						
22	Estonia 1995					

Table 5 The sum* and mean scores of time lag in year of introduction after the corresponding year of introduction in the first of the countries for the six studied pharmaceuticals

Country	Sum scores DOI-data† (years)	Mean score DOI-data† (years)	Sum scores registration data (years)	Mean score registration data (years)
United Kingdom	17	2.8	9	1.5
The Netherlands	21	3.5	8	1.3
Germany	22	3.7	27	4.5
France	13	2.2	n.a.	1.5‡
Spain	38	6.3	12	2
Estonia	87	14.5	72	12
Sweden	25	4.2	13	2.2

*Sum score, total lag compared with first country, six pharmaceuticals.
†Indications of start of diffusion of innovation.
‡Based on data for four pharmaceuticals.
n.a., not applicable.

Table 6 The diffusion period* of selected medical innovations

Innovation	Country	Start of diffusion (year)	Half of peak level (year)	Peak level (year)	Diffusion period (number of years)
Treatment of testicular cancer with cisplatin	Germany	1973	n.d.	2001	28
	Estonia	1995	2000	2005	10
	Sweden	1981	n.d.	1984	3
Treatment of peptic	Estonia	1993	n.d.	2000	7
ulcer with cimetidine	Sweden	1978	1982	1986	8
Treatment of breast cancer with tamoxifen	The Netherlands	1981	n.d.	2002	21
	Germany	1981	n.d.	2002	20
	Estonia	1992	n.d.	2003	11
	Sweden	1976	1984	1996	20
Treatment of colorectal cancer with oxaliplatin	Estonia	1999		2008	9
	Sweden	1999	2004	2008	9
Immunosuppressive treatment with	The Netherlands	1983	1998	1999	16
cyclosporine for kidney transplantation	Estonia	1993	2001	2008	15
	Sweden	1983	1991	1999	16
Treatment of HIV with zidovudine)	Sweden	1988	1993	1997	9

*Period between the year of the first indication of the start of diffusion (as presented in Table 2) and the year of the peak of sales level of the pharmaceutical in each country.
n.d., not detected during the data period available.

These results are consistent with the aspiration by 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 very successful at first, was replaced in 1987 by the Concertation Procedure, which in turn was replaced in 1995 by the European Medicines Evaluation Agency [78].

Estonia is an obvious outlier, reflecting its isolation from international commerce before 1991. Once Estonia regained its independence, it became integrated with the global economy, especially since acceding to the EU in 2004, and has seen sustained improvements in health care [79,80].

In general, innovative drugs were first introduced in the Netherlands, the United Kingdom and in France, whether assessed by date of registration or other indicators of when diffusion started. The process was generally delayed in Spain, especially when indicators of when diffusion started were considered. The delay in Sweden was somewhat larger when assessed by the start of diffusion than registration. Importantly, these findings demonstrate that registration does not always coincide with uptake of drugs, even though most attention so far has been on the former [5,6]. Thus, it is necessary to look at other characteristics of the health system to explain why some European citizens wait longer to receive innovative treatments than others [7,8], especially given the success of harmonization of the registration process [9].

Of the more recently introduced pharmaceuticals; oxalaplatin 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 using national licenses, before the Concertation Procedure became mandatory for HIV/AIDS treatments. For these pharmaceuticals, the variation in timing in introduction was low among the countries, including Estonia.

For tamoxifen, there was a time lag in several countries between the registration of the drug and its use in clinical trials. At that time, several therapeutical strategies were being discussed and its role of Tamoxifen seems not to have been clearly defined. Scientific papers at that time argue that it had a limited role [81] and called for more clinical trials [82], which started in most of the countries in this study in the late 1970s and 1980s.

To define the start of the diffusion process, one needs empirical longitudinal data on the uptake of drugs, such as sales statistics. However, in most cases, these were only available for recent years when the drugs were already registered for some years. Thus, sales statistics were mainly used to verify that the drug had diffused. Instead, diffusion was often considered to have begun with the first clinical trials in each country, provided indicators of a continued diffusion were available. For tamoxifen and antiretroviral drugs, clinical trials started when the drugs was already registered. In these cases, there may also have been less well documented use of the drug in some countries not captured by the search for clinical trials so the variation between countries should therefore be interpreted with caution.

There were several indications of a continued diffusion of the different innovations.

For several innovations, the length of period of diffusion seems to be similar among the countries according to sales statistics. This was the case for treatment with cimetidine, oxalaplatin and cyclosporine. For these pharmaceuticals, variations in use may instead reflect variation in the start of the diffusion among the countries.

In most cases ,there was a time lag of between 7 and 17 years from the introduction until guidelines were published. Thus, the presence of clinical guidelines would not reflect an early phase of the diffusion of innovation promoted by innovators and early adaptors. A previous review have found that the mean compliance rate for guidelines was 54% 3 years after the publication. Thus, it seems as if the publication of guidelines may reflect the phase when the innovation diffuses from the early majority to the late majority.

This would be in line with the theory of diffusion of innovation, where the late majority is considered to be more conservative and will not adopt an innovation until it is standard practice [11]. Several modifiable reasons have been found for not using proven pharmaceutical interventions, including clinician, patient and system factors [83]. Thus, it may be possible to influence the implementation of a pharmaceutical innovation in order to limit the variation in introduction and diffusion.

Implications for evaluation of medical care

In order to establish a new medical drug in medical practice, its efficacy must be proved in clinical trials and the drug must be approved by the regulatory authorities based on data on efficacy and safety. Efficacy refers to the potential of improving health of the patients under ideal conditions [84] of use, which should be the case in clinical trials. The pharmaceuticals studied in this paper have all passed this phase of assessment and have been approved for use in medical practice.

However, we must also consider that the effectiveness, defined as what is achieved under ordinary conditions, may vary [84]. There may be variation in the uptake of pharmaceuticals and other medical interventions and the quality of care may differ. Thus, the outcome of medical care may differ from what would be expected from the results of clinical trials. As pointed out by Brook and Lohr [84], there is need to integrate the concepts of efficacy, effectiveness, variations in population-based rates of use and quality of care when building models for policy, planning and evaluation of medical care.

In order to assess the impact on populations health of a new medical drug, we have to be able to measure the timing of introduction of the new drug as well as the diffusion process [11]. This information should then be linked to population outcome measures, in order to assess whether the new treatment has been effective in improving the health of the population [27].

Although the introduction of a new drug may be regarded as the date of registration, this paper has shown that the year when the drug was first used in medical care often differs from the official registration year. According to the theory of diffusion of innovations [11], the medical intervention may be introduced by innovators but in order to have a broader impact on populations health, there must also be a continued diffusion of the innovation. When applying this concept, we found that the registration year of the pharmaceuticals studied may differ from the year of introduction with a range between 11 years before and after the registration year. In assessing any impact on population health, therefore, the key issue is when the drug came into widespread use.

However, although we used a wide range of data in order to ascertain the introduction and diffusion of new innovations, our main finding is the need for harmonized data in EU countries. The lack of data on different phases of the diffusion process limited the possibilities to analyse the impact of introduction and diffusion of the new drugs.

Data on the diffusion of drugs and not simply the registration year should routinely be documented in a comparable way across the EU. This is most likely going to require prescribing data, which at present is inconsistent and only some elements are in the public domain. This should, ideally, include information on the indications for prescribing, although clearly, this will not be possible for some time, except where functioning patient information systems at a population level exist. It will also be important to use harmonized measures of the amount of drugs prescribed, such as the DDD [42]. Such improvements in the information on the introduction and diffusion of drugs would be a valuable tool in evaluating and planning health care.

Conclusions

Several pharmaceuticals first available in the 1970s and 1980s were introduced fairly simultaneously in most countries with the exception for Soviet era Estonia, in which the introduction was delayed until the 1990s. The delay in introducing the pharmaceuticals was shortest in France, the Netherlands and United Kingdom. This was true both for year of registration and first indicators of diffusion of the drugs, suggesting that delays are not only due to differences in the processes of registration. However, comparisons are challenging and there is a need for improved information on the introduction and diffusion of therapeutic innovations to inform comparisons of health system performance.

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References

1. World Health Report (2000) Health Systems: Improving Performance. Geneva: World Health Organization.
2. Marmot, M. (2005) Social determinants of health inequalities. *Lancet*, 365, 1099–1104.
3. Andersson, F. (1992) The drug lag issue: the debate seen from an international perspective. *Journal of Health Services*, 22 (1), 53–72.
4. Parker, J. (1989) Who has a drug lag? *Managerial and Decision Economics*, 10, 299–309.
5. Berlin, H. & Jönsson, B. (1986) International dissemination of new drugs: a comparative study of six countries. *Managerial and Decision Economics*, 7, 235–242.
6. Curries, W. J. (1990) European registration: today, tomorrow and beyond. *Journal of Clinical Pharmacology*, 30 (5), 386–389.
7. Cohen, J., Faden, L., Predaris, S. & Young, B. (2007) Patient access to pharmaceuticals: an international comparison. *The European Journal of Health Economics*, 8 (3), 253–266.
8. Atun, R. A. & Gurol-Urganci, I. & Sheridan, D. (2007) Uptake and diffusion of pharmaceutical innovations in health systems. *International Journal of Innovation Management*, 11 (2), 299–321. London and Hackensack: World Scientific Publishing Co. Pte. Ltd.
9. Abraham, J. & Levis, G. (1999) harmonising and competing for medicines regulation: how healthy are the European Union's systems of drug approval? *Social Science and Medicine*, 48, 1655–1667.
10. Rogers, E. M. (1962) Diffusion of Innovations. Free Press of Glencoe. London: Macmillan. New York.
11. Rogers, E. M. (2003) Diffusion of Innovations, 5th edn. New York, NY: Simon & Schuster.
12. Stanley, A., DeLia, D. & Cantor, J. C. (2007) Racial disparity and technology diffusion: the case of cardioverter defibrillator implants, 1996–2001. *Journal of the National Medical Association*, 99, 201–207.
13. Ferris, T. G., Kuhlthau, K., Ausiello, J., Perrin, J. & Kahn, R. (2006) Are minority children the last to benefit from a new technology? Technology diffusion and inhaled corticosteroids for asthma. *Medical Care*, 2006, 81–86.
14. Groenveld, P. W., Laufer, S. B. & Garber, A. M. (2005) Technology diffusion, hospital variation and racial disparities among elderly Medicare beneficiaries:1989–2000. *Medical Care*, 43, 320–329.
15. Levine, R. S., Briggs, N., Kilbourne, B. S., King, W. D., Fry-Johnson, Y., Baltrus, P. T. & Husaini, B. A. (2007) Black-White mortality from HIV in the United States before and after introduction of highly active antiretroviral therapy in 1996. *American Journal of Public Health*, 97, 1884–1892.
16. European Secondary Study Group (1996) Translation of clinical trials into practice. A European population-based study of the use of thrombolysis for acute myocardial infarction. *Lancet*, 347, 1203–1207.
17. Dray-Spira, R. & Lert, F. (2003) Social health inequalities during the course of chronic HIV disease in the era of highly active antiretroviral therapy. *AIDS (London, England)*, 17 (3), 283–290.
18. Oh, E. H., Imanaka, Y. & Evans, E. (2005) Determinants of t he diffusion of computed tomography and magnetic resonances imaging. *International Journal of Technology Assessment in Health Care*, 21, 73–80.
19. Lichtenberg, F. R. (2005) The impact of new drug launches on longevity: evidence from longitudinal, disease-level data from 52 countries 1982–2001. *International Journal of Health Care Finance and Economics*, 5, 47–73.
20. Packer, C., Simpson, S. & Stevens, A. (2006) International diffusion of new health technologies: a ten-country analysis of six helath technologies. *International Journal of Technology Assessment in Health Care*, 22, 419–428.
21. Rigter, H. & Bos, M. A. (1990) The diffusion of organ transplantation in Western Europe. *Healath Policy*, 16, 133–145.
22. Sejr, T., Andersen, T. F., Madsen, M., Roepstorff, C., Bide, T., Bay-Nielsen, H., Blais, R. & Holst, E. (1991) Prostatectomy in Denmark. Regional variation and the diffusion of medical technology 1977–1985. *Scandinavian Journal of Urology and Nephrology*, 25, 101–106.
23. Vanderveen, K. A., Paterniti, D., Kravitz, R. L. & Bold, R. J. (2007) Diffusion of surgical techniques in early stage breast cancer: variables related to adoption and implementation of sentinel lynph node biopsy. *Annals of Surgical Oncology*, 14, 1662–1669.
24. Rappaport, K. M., Forrest, C. B. & Holtzman, N. A. (2004) Adoption of liquid-based cervical cancer screening tests by family physicians and gynecologists. *Health Services Research*, 39, 927–947.
25. Jacob, R. & McGregor , M. (1997) Assessing the impact of health technology assessment. *International Journal of Technology Assessment in Health Care*, 13, 68–80.
26. Booth-Clibborn, N. P. C. & Stevens, A. (2000) Health technology diffusion rates. Statins, coronary stents, and MRI in England. *International Journal of Technology Assessment in Health Care*, 2000, 781–786.
27. Plug, I., Hoffmann, R. & Mackenbach, J. (eds). AMIEHS. Avoidable mortality in the European Union: towards better indicators for the effectiveness of health systems. Final report. Rotterdam: Department of Public Health, Erasmus MC, 2011. Available at: http://amiehs.lshtm.ac.uk/ (last accessed 24 May 2012).
28. Rutstein, D., Berenberg, W., Chalmers, T., Child, C., Fishman, A. & Perrin, E. (1976) Measuring the quality of medical care. *The New England Journal of Medicine*, 294, 582–588.
29. Nolte, E. & McKee, M. (2004) Does Healthcare Save Lives? Avoidable Mortality Revisited. London: The Nuffield Trust.
30. Mackenbach, J. P., Bouvier-Colle, M. H. & Jougla, E. (1990) 'Avoidable'mortality and health services: a review of aggregate data studies. *Journal of Epidemiology and Community Health*, 44, 106–111.
31. Charlton, J. R. H. & Velez, R. (1986) Some international comparisons of mortality amenable to medical intervention. *British Medical Journal (Clinical Research Ed.)*, 292, 295–300.
32. Westerling, R. (1992) Trends in 'avoidable' mortality in Sweden 1974–85. *Journal of Epidemiology and Community Health*, 46, 489–493.
33. Mackenbach, J. P., Kunst, A. E., Looman, C. W., Habbema, J. D. & van der Maas, P. J. (1988) Regional differences in mortality from conditions amenable to medical intervention in The Netherlands: a comparison of four time periods. *Journal of Epidemiology and Community Health*, 42, 325–332.
34. Neal, R. D., Stuart, N. & Wilkinson, C. (2007) Testicular cancer: seminoma. *Clinical Evidence (Online)*, 1807.
35. Barer, D., Ogilvie, A., Henry, D., *et al.* (1983) Cimetidine and tranexamic acid in the treatment of acute upper-gastrointestinal-tract bleeding. *The New England Journal of Medicine*, 308, 1571–1575.
36. Burleson, R., Kronhaus, R., Marbarger, P. & Jones, D. (1982) Cimetidine, posttransplant peptic ulcer complications, and renal allograft survival: a clinical and investigational perspective. *Archives of Surgery*, 117, 933–935.

37. Early Breast Cancer Trialists' Collaborative Group (1998) Tamoxifen for early breast cancer: an overview of the randomised trials. *The Lancet*, 351 (9114), 1451–1467.
38. Ferguson, R. M., Rynasiewicz, J. J., Sutherland, D. E., Simmons, R. L. & Najarian, J. S. (1982) Cyclosporin A in renal transplantation: a prospective randomized trial. *Surgery*, 92 (2), 175–182.
39. Hind, D., Tappenden, P., Tumur, I., Eggington, S., Sutcliffe, P. & Ryan, A. (2008) The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation. *Health Technology Assessment*, 12.
40. Levi, F., Zidani, R. & Misset, J. (1997) Randomised multicentre trial of chronotherapy with oxaliplatin, fluorouracil, and folinic acid in metastatic colorectal cancer. *Lancet*, 350, 681–686.
41. Fischl, M. A., Richman, D. D., Grieco, M. H., *et al*. (1987) The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. *The New England Journal of Medicine*, 317 (4), 185–191.
42. Maxwel, M., Heaney, D., Howie, J. G. R. & Noble, S. (1993) General practice fundholding: observations on prescribing patterns and costs using the defined daily dose method. *BMJ (Clinical Research Ed.)*, 307, 1190–1194.
43. Medical Research Council Working Party on Testicular Tumours (1985) Prognostic factors in advanced non-seminomatour germ-cell testicular tumours: results of a multicentre study. *The Lancet*, 325, 8–11.
44. Stoter, G., Sleijfer, D. T., Vendrik, C. P., Schraffordt Koops, H., Struyvenberg, A., Van Oosterom, A. T., Brouwers, T. M. & Pinedo, H. M. (1979) Combination chemotherapy with cis-diammine-dichloro-platinum, vinblastine, and bleomycin in advanced testicular non-seminoma. *Lancet*, 313, 941–945.
45. Osieka, R., Bruntsch, U., Gallmeier, W. M., Seeber, S. & Schmidt, C. G. (1976) Cis-Diamino-dichloro-platinum (II) in the treatment of otherwise treatment-resistant malignant testicular teratoma. *Deutsche Medizinische Wochenschrift (1946)*, 101, 191–195, 99 (in German).
46. Flamant, F., Schwartz, L., Delons, E., Caillaud, J. M., Hartmann, O. & Lemerle, J. (1984) Nonseminomatous malignant germ cell tumors in children. Multidrug therapy in Stages III and IV. *Cancer*, 54 (8), 1687–1691.
47. Aass, N., Klepp, O., Cavallin-Stahl, E., Dahl, O., Wicklund, H., Unsgaard, B., Baldetorp, L., Ahlstrom, S. & Fossa, S. D. (1991) Prognostic factors in unselected patients with nonseminomatous metastatic testicular cancer: a multicenter experience. *Journal of Clinical Oncology*, 9, 818–826.
48. Zwaveling, A. (1985) Soebhag R.Testicular tumors in the Netherlands. *Cancer*, 1, 1612–1617.
49. Mann, J. R., Pearson, D., Barrett, A., Raafat, F., Barnes, J. M. & Wallendszus, K. R. (1989) Results of the United Kingdom Children's Cancer Study Group's malignant germ cell tumor studies. *Cancer*, 63, 1657–1667.
50. Huddart, S. N., Mann, J. R., Gornall, P., Pearson, D., Barrett, A., Raafat, F. & Barnes, J. M. (1990) Wallendsus KR.The UK Children's Cancer Study Group: testicular malignant germ cell tumours 1979–1988. *Journal of Pediatric Surgery*, 25, 406–410.
51. Eckardt, V. F., Kanzler, G., Willems, D., Feyerabend, H., Backwinkel, K. P., Hentschel, E., Schütze, K. & Schwamberger, K. (1982) Treatment of duodenal ulcer with cimetidine: comparison of two dosage regimens. *Deutsche Medizinische Wochenschrift (1946)*, 107, 60–62 (in German).
52. Galmiche, J. P., Bernades, P., Capron, J. P., *et al*. (1979) Cimetidine versus combined therapy (antacid, anticholinergic drugs and oxyferriscorbone sodique) in short-term treatment of gastric and duodenal ulcer. A multicenter controlled trial. *Gastroenterologie Clinique et Biologique*, 3 (4), 355–361 (in French).
53. Galmiche, J. P., Colin, R., Hecketsweiler, P., Le Grix, A., Métayer, P., Le Bihan, M., Ténière, P. & Geffroy, Y. (1978) Treatment of bleeding due to peptic ulcer with cimetidine. A double blind trial. *Gastroenterologie Clinique et Biologique*, 2, 771–776 (in French).
54. Gilsanz, V., Rebollar, J. L., Chantres, M. T., Rosso, C., Pérez Oteyza, C. & Ballarin, M. (1980) Cimetidine in the treatment of gastric ulcer. Double blind study. *Revista Clinica Espanola*, 158, 57–60 (in Spanish).
55. Rutqvist, L. E., Cedermark, B., Glas, U., Johansson, H., Nordenskjöld, B., Skoog, L., Somell, A., Theve, T., Friberg, S. & Askergren, J. (1987) The Stockholm trial on adjuvant tamoxifen in early breast cancer. Correlation between estrogen receptor level and treatment effect. *Breast Cancer Research and Treatment*, 10 (3), 255–266.
56. Rutqvist, L. E., Cedermark, B., Fornander, T., *et al*. (1989) The relationship between hormone receptor content and the effect of adjuvant tamoxifen in operable breast cancer. *Journal of Clinical Oncology*, 7 (10), 1474–1484.
57. European Multicenter Traíal Group (1983) Cyclosporin in cadaveric renal transplantation: one-year follow-up of a multicentre trial. *The Lancet*, 2, 986–989.
58. Salaman, J. R., Gomes Da Costa, C. A. & Griffin, P. J. (1987) Renal transplantation without steroids. *The Journal of Pediatrics*, 111, 1026–1028.
59. Andreu, J., Ricart, M. J., Oppenheimer, F., Vilardell, J. & Sans, A. (1988) The efficacy of low doses of cyclosporine A plus azathioprine. *Transplantation Proceedings*, 20 (Suppl. 6), 28–29.
60. Lundgren, G., Groth, C. G., Albrechtsen, D., *et al*. (1986) HLA-matching and pretransplant blood transfusions in cadaveric renal transplantation – a changing picture with cyclosporin. *Lancet*, 2, 66–69.
61. de Gramont, A., Figer, A., Seymour, M., *et al*. (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *Journal of Clinical Oncology*, 18, 2938–2947.
62. Díaz-Rubio, E., Sastre, J., Zaniboni, A., Labianca, R., Cortés-Funes, H., de Braud, F., Boni, C., Benavides, M., Dallavalle, G. & Homerin, M. (1998) Oxaliplatin as single agent in previously untreated colorectal carcinoma patients: a phase II multicentric study. *Annals of Oncology*, 9, 105–108.
63. Levi, F., Perpoint, B., Garufi, C., *et al*. (1993) Oxaliplatin activity against metastatic colorectal cancer. A phase II study of 5-day continuous venous infusion at circadian rhythm modulated rate. *European Journal of Cancer*, 29A, 1280–1284.
64. Poston, G. J. (2005) The use of irinotecan and oxaliplatin in the treatment of advanced colorectal cancer. *European Journal of Surgical Oncology*, 31, 325–330.
65. Saunders, M. P. & Valle, J. W. (2002) Why hasn't the National Institute been 'NICE' to patients with colorectal cancer? *British Journal of Cancer*, 86, 1667–1669.
66. Graeven, U. & Schmiegel, W. (2000) Colon carcinoma. Consensus of therapeutic strategies. *Der Internist*, 41, 876–885 (in German).
67. Swedish Drug Sales Statistics. Apotek AB (The National Corporation of Swedish Pharmacies) 1977–2008. Stockholm, Sweden.
68. Ragnhammar, P., Hafström, L., Nygren, P. & Glimelius, B. (2001) SBU-group. Swedish Council of Technology Assessment in Health Care.A systematic overview of chemotherapy effects in colorectal cancer. *Acta Oncologica (Stockholm, Sweden)*, 40, 282–308.
69. Perenboom, R., Reiss, P., Danner, S. A. & van 't Wout, J. W. (1990) Zidovudine therapy in 141 patients with symptoms of HIV infection; a multicenter study. *Nederlands Tijdschrift Voor Geneeskunde*, 134, 120–124 (in Dutch).
70. Cohen, J. (1993) Early AZT takes a pounding in French-British 'Concorde' trial. *Science*, 260, 157.

71. White, I. R., Walker, S., Babiker, A. G. & Darbyshire, J. H. (1997) Impact of treatment changes on the interpretation of the Concorde trial. *AIDS (London, England)*, 11, 999–1006.
72. German AIDS Study Group (1994) Survival of patients receiving zidovudine before or after AIDS diagnosis: results of a German multicenter study. *The Clinical Investigator*, 72, 111–116.
73. Concorde Coordinating Committee (1994) Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. *Lancet*, 343, 871–881.
74. Katlama, C., Ingrand, D., Loveday, C., Clumeck, N., Mallolas, J., Staszewski, S., Johnson, M., Hill, A. M., Pearce, G. & McDade, H. (1996) Safety and efficacy of lamivudine-zidovudine combination therapy in antiretroviral-naive patients. A randomized controlled comparison with zidovudine monotherapy. Lamivudine European HIV Working Group. *JAMA: The Journal of the American Medical Association*, 276, 118–125.
75. Nordic Medical Research Councils' HIV Therapy Group (1992) Double blind dose-response study of zidovudine in AIDS and advanced HIV infection. *BMJ (Clinical Research Ed.)*, 304, 13–17.
76. Brettle, R. P., Burns, S. B., Povey, S., Leen, C. L. & Welsby, P. D. (1997) British HIV Association guidelines for antiretroviral treatment of HIV seropositive individuals. *Lancet*, 349, 1837–1838.
77. Miró, J. M., Antela, A., Arrizabalaga, J., *et al*. (2000) Recommendation of GESIDA (AIDS Study Group)/National Plan on AIDS with respect to the anti-retroviral treatment in adult patients infected with the human immunodeficiency virus in the year 2000 (I). *Enfermedades Infecciosas Y Microbiologia Clinica*, 18, 329–351 (in Spanish).
78. Jefferys, D. B. & Jones, K. H. (1995) EMEA and the new pharmaceutical procedures for Europe. European Medicines Evaluation Agency. *European Journal of Clinical Pharmacology*, 47 (6), 471–476.
79. Atun, R. A., Menabde, N., Saluvere, K., Jesse, M. & Habicht, J. (2006) Introducing a complex health innovation–primary health care reforms in Estonia (multimethods evaluation). *Health Policy*, 79, 79–91.
80. Koppel, A., Kahur, K., Habicht, T., Saar, P., Habicht, J. & van Ginneken, E. (2008) Estonia: health system review. *Health Systems in Transition*, 10 (1), 1–230. Available at: http://www.euro.who.int/__data/assets/pdf_file/0011/80687/E91372.pdf (last accessed 17 March 2014).
81. Tagnon, H. J. (1977) Antiestrogens in treatment of breast cancer. *Cancer*, 39 (6 Suppl.), 2959–2964.
82. Mouridsen, H. T. & Palshof, T. (1980) Principles and indications of endocrine treatment of advanced breast cancer. *Recent Results in Cancer Research. Fortschritte Der Krebsforschung. Progres Dans Les Recherches Sur Le Cancer*, 71, 112–117.
83. Barry, A. R., Loewen, P. S., de Lemos, J. & Lee, K. G. (2012) Reasons for non-use of proven pharmacotherapeutic interventions: systematic review and framework development. *Journal of Evaluation in Clinical Practice*, 18 (1), 49–55.
84. Brook, R. H. & Lohr, K. N. (1985) Efficacy, effectiveness, variations, and quality. *Medical Care*, 23 (5), 710–722.
85. Ribeiro, G. & Swindell, R. (1992) The Christie Hospital adjuvant tamoxifen trial. *National Cancer Institute Monograph*, 11, 121–125.
86. Beex, L., Burghouts, J., van Turnhout, J., *et al*. (1987) Oral versus im administration of high-dose medroxyprogesterone acetate in pre-treated patients with advanced breast cancer. *Cancer Treatment Reports*, 71 (12), 151–156.
87. Bellmunt, J. & Solé, L. (1991) European early phase II dose-finding study of droloxifene in advanced breast cancer. *American Journal of Clinical Oncology*, 14 (Suppl. 2:S), 36–39.
88. Jansen, R. L., Sylvester, R., Sleyfer, D. T., *et al*. (1991) Long-term follow-up of non-seminomatous testicular cancer patients with mature teratoma or carcinoma at postchemotherapy surgery. EORTC Genitourinary Tract Cancer Cooperative Group (EORTC GU Group). *European Journal of Cancer*, 27, 695–698.
89. Haayer, F. M., van der Werf, G. T., Wieringa, N. F. & Wesseling, H. (1983) Use of cimetidine; parallels and discrepancies between the views of drug regulatory agencies and practicing physicians. *European Journal of Clinical Pharmacology*, 25, 601–607.
90. Gilks, W. R., Bradley, B. A. & Gore, S. M. (1990) Cyclosporine: its time of impact on kidney graft survival. *Transplantation Proceedings*, 22, 2282.
91. Henny, F. C., Kootte, A. M., Moolenaar, A. J., van Es, L. A. & Paul, L. C. (1987) A prospective study on the influence of cyclosporine and azathioprine on renal allograft survival and function. *Transplantation Proceedings*, 19, 1853–1855.
92. Hourmant, M., Buzelin, F., Dubigeon, P. & Soulillou, J. P. (1987) High long-term graft survival rates in kidney transplantation with the sequential association of antithymocyte globulin and cyclosporine A monotherapy. *Transplantation Proceedings*, 19, 2113–2114.
93. Grupo de estudio de la sociedad española de nefrología (1988) El emplo de ciclosporina en nefropatías glomerulares. *Datos de 61 enfermos incluidos en el Estudio Cooperativo de la Sociedad Española de Nefrología*, 8 (Suppl. 1), 15–23 (in Spanish).
94. Linder, R., Restifo, A. C., Lindholm, A. & Groth, C. G. (1991) Long-term cyclosporine A treatment does not progressively impair renal graft function: a 5-year follow-up study. *Transplantation Proceedings*, 23, 2210.
95. Salzberger, B., Marcus, U., Vielhaber, B., Arasteh, K., Gölz, J., Brockmeyer, N. H. & Rockstroh, J. (2004) German-Austrian recommendations for the antiretroviral therapy of HIV-infection (status May 2004). *European Journal of Medical Research*, 9, 491–504.
96. Gisslén, M., Ahlqvist-Rastad, J., Albert, J., Blaxhult, A., Hamberg, A. K., Lindbäck, S., Sandström, E. & Uhnoo, I. (2006) Swedish Consensus Group.Antiretroviral treatment of HIV infection: Swedish recommendations 2005. *Scandinavian Journal of Infectious Diseases*, 38, 86–103.
97. Lindbäck, S., Vizzard, J., Cooper, D. A. & Gaines, H. (1999) Long-term prognosis following zidovudine monotherapy in primary human immunodeficiency virus type 1 infection. *The Journal of Infectious Diseases*, 179, 1549–1552.