Decreasing trends in incidence and prevalence of renal replacement therapy in Croatia from 2000 to 2009

Svjetlana Čala on behalf of the Croatian Registry of Renal Replacement Therapy

Nephrology and Dialysis Department, University Clinic for Internal Diseases, Sestre Milosrdnice Clinical Hospital Centre, School of Medicine, University of Zagreb, Zagreb, Croatia

Correspondence and offprint requests to: Svjetlana Čala; E-mail: svjetlana.cala@gmail.com

Abstract

Background. Recent studies have indicated stabilization in the incidence rates of renal replacement therapy (RRT) for end-stage renal disease (ESRD) in a number of European countries, the USA, and Japan. The aim of this study was to provide an update on the incidence and prevalence trends of RRT in Croatia over the past decade.

Methods. Data from the Croatian Registry of Renal Replacement therapy from 2000 to 2009 were analysed. Trends in incidence and prevalence were examined using the Poisson regression and Joinpoint regression analysis.

Results. The total adjusted incidence rate of RRT for ESRD increased from 106.1 per million population (pmp) in 2000 to 140.4 pmp in 2004, at annual percentage change (APC) 7.0% (95% confidence interval (CI) 1.8, 12.6). From 2004 to 2009, there was no rise in incidence [APC −1.0 (95% CI −4.5, 2.6)]. Continuous growth in incidence was present only in males [APC 2.6 (95% CI 0.9, 4.4)], in patients 65 years and older [APC 5.5 (95% CI 3.4, 7.6)], in patients with diabetes [APC 2.4 (95% CI 0.5, 4.4)], hypertension/renovascular disease [APC 6.1 (95% CI 1.6, 10.8)] and unknown/missing diagnosis [APC 13.8 (95% CI 9.0, 18.8)]. The total adjusted prevalence rate rose from 598.7 pmp in 2000 to 785.6 pmp in 2004, at an annual rise of 7.5% (95% CI 5.8, 9.3). In the 2004–09 period, the growth of RRT slowed to APC 2.4 (95% CI 1.2, 3.5), and reached 890.8 pmp in 2009.

Conclusions. After a rapid increase in the incidence of RRT in Croatia from 2000 to 2004, the incidence rate has stabilized during the 2004–09 period. The stabilization of incidence is followed by a reduction in the growth in prevalence rate. The stabilization of RRT incidence could be attributed to the successful prevention and treatment of cardiovascular diseases that simultaneously improved renal survival.

Keywords: Croatia; incidence trends; prevalence trends; renal replacement therapy

Introduction

A continuous rise in renal replacement therapy (RRT) incidence of 5–8% per year has been predicted for developed countries, and an even higher increase has been expected in less developed parts of the world [1, 2]. The first sign of a more favourable scenario came from the USA after years of considerable growth, where the rate of new patients taken into RRT began to decrease between 2002 and 2004. The overall incidence rate adjusted for age and sex declined by 1.1% and reached 339 per million population (pmp) [3]. This incidence stabilization trend in the USA attracted much attention, as epidemiological occurrences in the USA have been shown to precede and predict future trends in other parts of the world with developed RRT.

Trends of stabilization of RRT incidence rates in some European countries were reported for the first time in 2004 [4] and confirmed in publications in the following years [5, 6]. The incidence rates in European countries are stabilizing at ~125 pmp, less than half of that observed in the USA at the time of the halting incidence growth.

Australia has experienced a 2.1% reduction at an incidence rate of 95 pmp, and New Zealand had a 7.6% reduction at an incidence rate of 110 pmp in 2004 [7]. In Canada, a slowing rise in incidence was observed in 2004. A maximal incidence rate of 168 pmp was attained in 2007, followed by a decrease thereafter, as reported by the Canadian Organ Replacement Register [8].

A stabilization and drop in the incidence of RRT has been observed recently even in the countries with the highest incidence rates [9, 10]. The incidence rate in Taiwan in 2009 (347 pmp) was the lowest observed from 2001 [10]. In Japan in 2009, the incidence rate was 287 pmp, for the first time it was lower than the preceding year [10].
Interestingly, stabilizations in incidence occurred in a relatively short time frame in various countries, but at very different incidence rates, from less than 100 pmp to over 370 pmp.

Our study examines the incidence and prevalence of RRT in Croatia during the 2000–09 period, looking for changes in trends that might predict a decrease in burden of RRT.

Materials and methods

The National Health System covers the costs of dialysis and transplantation for all citizens of Croatia. All patients on RRT for end-stage renal disease (ESRD), children and adults included, have been registered with the Croatian Registry of Renal Replacement Therapy (CRRRT) since 2000 [11]. Dialysis and transplant centres participate voluntarily, with complete coverage of all patients treated by haemodialysis, peritoneal dialysis and transplantation.

The data collected include the identification parameter, gender, date of birth, date of start of RRT, primary renal disease according to the ERA-EDTA coding system, type of treatment, date of change of treatment, and date and cause of death. The incidence of RRT was defined as the number of patients starting treatment during a year and alive on RRT at Day 91, and the prevalence was defined as the number of patients receiving RRT on 31 December. The incidence rate and the prevalence rate were calculated by dividing the incident and prevalent number with the mid-year population of Croatia in millions (pmp) or per million age related population (pmpar). Age- and gender-adjusted incidence and prevalence rates were calculated using the age and gender distribution of the mid-year population of Croatia. To correct for errors of late reporting, data were updated using the 2010 CRRT database. Statistical analysis was performed by SPSS version 10.0 (SPSS Inc., Chicago, IL) for Windows operating systems (Microsoft, Redmond, Washington, DC). Time trends were analysed with the Poisson regression and joinpoint regression methods [12]. An observation period of 10 years was tested for a maximum of two joinpoints.

Results

The population treated by RRT for ESRD in Croatia in the period 2000–09 is presented in Table 1.

Trends in the incidence of RRT in Croatia, 2000–09

The incidence of RRT at Day 91, the incidence rate and incidence rate adjusted for age and gender distribution are presented in Table 2. By joinpoint regression analysis, the year 2004 was identified as a breaking point in incidence trend. The annual percentage change (APC) of incidence during the 2000–04 period was 7.7 (95% CI 2.2, 13.5), and adjusted incidence rate was increasing during the same interval at an annual rate of 7.0% (APC; 95% CI 1.8, 12.6). The increase in incidence ceased in the 2004–09 period, as measured by incidence [APC = 0.2 (95% CI −3.9, 3.5)], incident rate [APC = −0.1 (95% CI −3.8, 3.7)] and adjusted incident rate [APC = 1.0 (95% CI −4.5, 2.6)].

Gender and incidence trends. In males, a constant growth in incidence was present throughout the decade. The average annual growth of male incidence was 3.8% (95% CI 2.0, 5.6), and for age-adjusted male incidence, it was 2.6% (95% CI 0.9, 4.4).

In females, the incidence of RRT did not change during the 2000–09 decade. The trend was not different from zero in female unadjusted incidence [APC = 2.0 (95% CI −0.0, 4.1)] and in female age-adjusted incidence [APC = 1.6 (95% CI −0.5, 3.7)].

The age-adjusted incidence rate in males was constantly higher than in females, by a factor of 1.4–1.8.

Age and incidence trends. The incidence trends according to age are presented in Table 3. In patients under 65 years of age, the incidence [APC = 0.8 (95% CI −1.9, 3.6)] and adjusted incidence [APC = 0.2 (95% CI −1.1, 1.5)] were stable during the observed period. No change in incidence was found in the age groups 0–19, 20–44 and 45–64 when analysed separately. In all patients aged 65 and over taken together, there was a constant increase in incidence during the 10-year period.

Table 1. Population on RRT in Croatia during the period 2000–09

| Year | Incident number | Incident pmp | Age (years), median | Primary renal disease (%) | Prevalent number | Prevalence pmp | Treatment mode (%) |
|------|----------------|--------------|---------------------|---------------------------|-----------------|---------------|-------------------|
| 2000 | 466            | 106          | 62                  | GN 17, PN 14, PKD 8        | 2613            | 592           | HD 81, PD 15, TX 15 |
| 2001 | 479            | 108          | 62                  | GN 17, PN 12, RD 7         | 2758            | 621           | HD 79, PD 15, TX 15 |
| 2002 | 495            | 111          | 62                  | GN 19, PN 12, RD 7         | 3134            | 699           | HD 76, PD 17, TX 17 |
| 2003 | 590            | 131          | 63                  | GN 15, PN 13, RD 6         | 3317            | 738           | HD 76, PD 17, TX 17 |
| 2004 | 629            | 140          | 65                  | GN 12, PN 12, RD 5         | 3541            | 787           | HD 74, PD 17, TX 19 |
| 2005 | 599            | 133          | 66                  | GN 16, PN 12, RD 5         | 3697            | 822           | HD 73, PD 20, TX 17 |
| 2006 | 571            | 127          | 67                  | GN 15, PN 14, RD 5         | 3835            | 853           | HD 71, PD 22, TX 22 |
| 2007 | 626            | 139          | 67                  | GN 15, PN 9, RD 7          | 3955            | 880           | HD 71, PD 23, TX 23 |
| 2008 | 609            | 136          | 67                  | GN 14, PN 11, RD 4         | 4036            | 899           | HD 69, PD 26, TX 26 |
| 2009 | 601            | 134          | 67                  | GN 10, PN 9, RD 5          | 4142            | 923           | HD 66, PD 28, TX 28 |

*GN*, glomerulonephritis; *PN*, pyelonephritis; *PKD*, polycystic kidney disease; *HT/RVD*, hypertension; *HD*, haemodialysis; *PD*, peritoneal dialysis; *TX*, transplantation renovascular disease; *No DG*, unknown or missing diagnosis.
follow-up. The adjusted incidence rate in 65+ grew constantly with an APC of 5.5 (95% CI 3.4, 7.6), although the number of incident patients after the fast growth in the initial 5-year period [APC 14.1 (95% CI 6.0, 22.9)] stabilized in the last 5 years [APC 2.2 (95% CI –1.8, 6.3)]. The rise in incidence in the age group 65–74 was constant with APC 4.4 (95% CI 2.7, 6.0). The highest APC of incidence was seen in patients aged 75 and older during the 2000–03 interval: APC 34.5 (95% CI 16.2, 55.8), but growth ceased in the 2003–09 period: APC 1.8 (95% CI –2.0, 5.7).

Primary renal disease and incidence trends. The trends in incidence and incidence rate at Day 91 according to primary renal disease are depicted in Table 4. Incidence, incidence rates and adjusted incident rates of RRT for renal failure caused by glomerulonephritis, pyelonephritis and polycystic kidney disease did not increase throughout the observed period. A constant increase in incidence and incidence rate was evident for patients with diabetes (adjusted incidence rate APC 2.4; 95% CI 0.5, 4.4) and hypertension/renovascular disease (adjusted incidence rate APC 6.1; 95% CI 1.6, 10.8) and for the group with unknown/missing diagnosis of primary renal disease (adjusted incidence rate APC 13.8; 95% CI 9.0, 18.8).

Trends in the prevalence of RRT in Croatia, 2000–09
The prevalence, prevalence rate and prevalence rate adjusted for age and gender distribution are presented in Table 5. A change in trend was observed in 2004. The overall adjusted prevalence increased from 598.7 pmp in 2000 to 785.6 pmp in 2004, at APC of 7.5 (95% CI 5.8, 9.3). From 2004 to 2009, the rate of increase slowed to APC 2.4 (95% CI 1.2, 3.5).

In males, the age-adjusted prevalence in the 2000–04 period increased with APC 7.7 (95% CI 5.7, 9.8), and growth slowed in the second 5-year period to APC 2.2 (95% CI 0.9, 3.6).

In females, the age-adjusted prevalence in the 2000–04 period had APC 7.2 (95% CI 5.1, 9.4) and in the 2004–09 period APC was 2.5 (95% CI 1.0, 3.9).

The age-adjusted prevalence in males was constantly higher than that of females by a factor of 1.4–1.5.

Discussion
From the year 2000, a registry of RRT with a complete coverage of the general population was recorded in Croatia. Data collected during the first decade, from 2000 to 2009, are the subject of this study with the aim to recognize the trends in incidence and prevalence of RRT in Croatia.

The incidence at Day 91 was chosen for presentation, as it has a stronger effect on the prevalence and on the burden of RRT for society.

The 2000–09 decade of RRT in Croatia was characterized by changes in the trends of incidence and prevalence that occurred in the middle of the observation period. During the first 5 years, the incidence (Day 91, age and gender adjusted) was increasing at a rate of 7.0% annually, and adjusted prevalence growth was 7.5%. In the following 5 years, the growth in incidence ceased, and the increase in prevalence reduced to 2.4%,
Table 3. Incidence at Day 91 of RRT in Croatia according to age during the period 2000–09

 Incidence by year

| Age     | 2000   | 2001   | 2002   | 2003   | 2004   | 2005   | 2006   | 2007   | 2008   | 2009   | Period | APC (%) | 95% CI Lower | 95% CI Upper |
|---------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|---------|-------------|-------------|
| 0–19    | 9      | 9      | 6      | 7      | 6      | 8      | 12     | 7      | 8      | 7      | 2000–09 | -0.2     | -4.9       | 4.7          |
| Incidence | 8.3    | 8.4    | 5.6    | 6.6    | 5.8    | 7.9    | 12     | 7.1    | 8.2    | 7.2    | 2000–09 | 1.1      | -3.7       | 6.2          |
| Incidence pmarp | 60     | 62     | 64     | 69     | 64     | 69     | 64     | 70     | 51     | 33.6   | 2000–09 | -0.6     | -2.6       | 1.5          |
| 20–44   | 214    | 208    | 222    | 238    | 251    | 215    | 231    | 206    | 236    | 205    | 2000–09 | -0.3     | -1.9       | 1.3          |
| Incidence | 193.7  | 185.4  | 194.7  | 206.2  | 195.2  | 172.4  | 195.2  | 167.5  | 169.4  | 2000–09 | -1.5     | -3.1       | 0.1          |
| Incidence pmarp | 150    | 146    | 143    | 180    | 203    | 186    | 183    | 195    | 192    | 201    | 2000–09 | 3.7*     | 1.9        | 5.6          |
| 45–64   | 345.6  | 318.1  | 319.9  | 400.0  | 452.1  | 417.0  | 416.9  | 451.4  | 452.8  | 489.1  | 2000–09 | 4.4*     | 2.7        | 6.0          |
| Incidence | 33     | 54     | 60     | 96     | 105    | 118    | 113    | 126    | 134    | 132    | 2000–03 | 41.9*    | 22.7       | 64.0         |
| Incidence pmarp | 140.4  | 218.6  | 229.9  | 351.6  | 365.9  | 393.3  | 358.7  | 385.3  | 395.3  | 377.1  | 2000–03 | 34.5*    | 16.2       | 55.8         |
| 65+     | 283    | 209    | 292    | 314    | 312    | 295    | 275    | 305    | 283    | 268    | 2000–09 | 0.8      | -1.9       | 3.6          |
| Incidence | 75.6   | 74.4   | 77.4   | 83.2   | 85.3   | 78.7   | 73.5   | 81.7   | 75.9   | 71.9   | 2000–09 | -0.3     | -1.6       | 1.0          |
| Incidence pmarp | 183    | 200    | 203    | 276    | 304    | 296    | 321    | 326    | 333    | 337    | 2000–04 | 14.1*    | 6.0        | 22.9         |
| 65+ Incidence | 274.0  | 291.1  | 287.1  | 381.7  | 405.7  | 395.2  | 382.6  | 422.4  | 437.3  | 477.1  | 2000–09 | 5.5*     | 3.4        | 7.6          |

*APC significantly different from zero.

Conclusion:

The trends of slowing incidence and prevalence of ESRD are global and seem to be unrelated to the level of income, and the extent of chronic kidney disease in a general population and the general health status of the population. The trends of slowing incidence and prevalence of ESRD are global and seem to be unrelated to the level of income, and the extent of chronic kidney disease in a general population and the general health status of the population. The trends of slowing incidence and prevalence of ESRD are global and seem to be unrelated to the level of income, and the extent of chronic kidney disease in a general population and the general health status of the population.
Hypertension/renovascular disease

*APC significantly different from zero.

The likely explanation for the evidence of stabilization in the incidence of RRT in Croatia is a combination of 10 years comprehensive RRT registry, unrestricted (unchanged) access to the RRT, and the decreasing trend in cardiovascular mortality (by 27.5%) during the same decade [17].

Conclusions

Croatia has attained the trend of stabilizing incidence of RRT for ESRD. The overall incidence of RRT did not increase from 2004 onwards. The incidence of RRT was stable over the 10-year period in females, aged under 65, for renal failure caused by glomerulonephritis and for pyelonephritis and polycystic kidney disease. An increase in incidence was constant in males, 65–74 age group, in ESRD caused by diabetes, hypertension/renovascular disease and in patients with unknown/missing diagnosis of kidney failure. As a consequence of the stabilizing overall incidence, the rise in prevalence decreased in 2004 to one-third of the growth present in the previous 5 years. Stabilization of the incidence of RRT in Croatia, as well as in other regions where it has been observed, might be the collateral effect of better prevention and treatment for cardiovascular diseases evidenced by a continuously declining cardiovascular mortality.

Acknowledgements. We would like to thank the patients and staff of all the dialysis and transplant units for contributing data to the Croatian Registry of Renal Replacement Therapy. We would also like to thank the persons actively engaged in collecting and referral of the data: Radosna-Dome Bareta, Nikolina Bašić Jukić, Žarko Belavić, Ivan Bogadi, Marina Bogdanović, Dijana Borić Škaro, Melita Bralda Trošija, Vinko Brozović, Ljubica Bubić Filipi, Dražen Buhaneć, Miroslav Crnogorac, Rak Ćivljak, Valentina Corić Martinović, Sonja Dits, Nevenka Đivić, Slava Đoko, Marina Đzamba, Vicka Đakov, Tomislav Filipović, Vladimir Gašparović, Danijela Petrović Germin, Snježana Glavaš Boras, Željka Grdan, Jasna Guel, Marijana Gulin, Branko Heinrich, Sonja Hodžić, Mario Ilić, Basiliška Iskra, Renata Ivanac Janković, Ana Ivekic Jambrošić, Marko Jakić, Nikola Janković, Vlatka Japec, Ivo Jelić, Ivan Jurakić, Dragom Klaric, Mladen Knotek, Ranko Ladavac, Jelenko Lazić, Mariza Lukić, Dubravka Marić, Gordana Marković, Senka Mašković, Stanka Meić, Iva Mesaros, Josip Meter, Dubravka Mihaljević, Karlo Mihovilić, Violeta Milić, Petar Milinović, Kristina Miočić, Kristijan Mužić, Mićana Nožinić Tatalović, Lidija Orlić, Pajica Pavković, Mario Pebar, Petar Petrić, Davor Podbevšek, Marina Potočnjak, Mladenka Primorac, Zvonko Puretić, Jasa Slaviček, Dubravka Smajlović, Marica Stjepandić, Milenko Sain, Sinisa Šefer, Ružica Šmalcević, Željko Šprem, Milena Tenčić, Tomislav Teskera, Krešimir Tomijenović, Jadranka Vidoš, Jadranka Vlasić Matas, Marijana Vukman, Velimir Vukšić, Vladko Wilhelm, Franka Zuban and Marijana Živko.

Conflict of interest statement. None declared.
### Table 5. Prevalence of RRT in Croatia during the period 2000–2009

| Period | Trend 1 | Trend 2 | 95% CI Lower | 95% CI Upper | APC (% Lower) | APC (% Upper) | 95% CI Lower | 95% CI Upper | APC (% Lower) | APC (% Upper) |
|--------|---------|---------|--------------|--------------|---------------|---------------|--------------|--------------|---------------|---------------|
| All    | 2000    | 2001    | 2002         | 2003         | 2004          | 2005          | 2006         | 2007         | 2008          | 2009          |
| Prevalence pmp | 2613 | 2758 | 3134 | 3317 | 3541 | 3697 | 3835 | 3955 | 4036 | 2000–04 | 8.4* | 6.5 | 10.3 | 2004–09 | 3.0* | 1.8 | 4.3 |
| Prevalence pmarp | 592.4 | 621.3 | 699.4 | 737.6 | 787.3 | 822.2 | 853.0 | 879.9 | 898.8 | 2000–04 | 7.9* | 6.1 | 9.6 | 2004–09 | 3.0* | 1.2 | 3.5 |
| Male    | 2000    | 2001    | 2002         | 2003         | 2004          | 2005          | 2006         | 2007         | 2008          | 2009          |
| Prevalence pmp | 1455 | 1539 | 1756 | 1848 | 1981 | 2096 | 2145 | 2208 | 2293 | 2344 | 2000–04 | 8.5* | 6.5 | 10.5 | 2004–09 | 3.2* | 1.9 | 4.6 |
| Prevalence pmarp | 683.7 | 719.2 | 816.9 | 855.8 | 917.5 | 969.8 | 993.0 | 1024.1 | 1056.1 | 1084.9 | 2000–04 | 8.1* | 6.2 | 10.1 | 2004–09 | 3.2* | 1.9 | 4.6 |
| Female  | 2000    | 2001    | 2002         | 2003         | 2004          | 2005          | 2006         | 2007         | 2008          | 2009          |
| Prevalence pmp | 1159 | 1222 | 1378 | 1473 | 1560 | 1602 | 1689 | 1746 | 1744 | 1798 | 2000–04 | 7.6* | 6.0 | 10.4 | 2004–09 | 2.7* | 1.3 | 4.2 |
| Prevalence pmarp | 507.4 | 530.5 | 591.8 | 628.4 | 667.1 | 685.7 | 723.5 | 748.3 | 748.3 | 772.1 | 2000–04 | 7.6* | 5.4 | 10.7 | 2004–09 | 2.9* | 1.5 | 4.4 |
| Male/Female | 1.4 | 1.4 | 1.5 | 1.4 | 1.4 | 1.4 | 1.4 | 1.4 | 1.4 | 1.4 | 1.4 | 1.4 | 1.4 | 1.4 |

*APC significantly different from zero.

Received for publication: 21.3.12; Accepted in revised form: 4.6.12

References

1. El Nahas AM, Bello AK. Chronic kidney disease: the global challenge. Lancet 2005; 365: 331–340
2. Lysaght MJ. Maintenance dialysis population dynamics: current trends and long-term implications. J Am Soc Nephrol 2002; 13: S37–S40
3. U.S. Renal Data System. USRDS 2006 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health. National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2006
4. Jager KJ. ERA-EDTA Registry Report 2004 (presentation). XLI ERA-EDTA Congress 2004, Lisbon, Portugal. Available at http://www.era-edta-reg.org/presentations.jsp
5. Jager KJ, van Dijk PC. Has the rise in the incidence of renal replacement therapy in developed countries come to an end? Nephrol Dial Transplant 2007; 22: 678–680
6. Kramer A, Stel V, Zoccali C et al. An update on renal replacement therapy in Europe: ERA-EDTA Registry data from 1997 to 2006. Nephrol Dial Transplant 2009; 24: 3557–3566
7. McDonald S, Excell L, Shtantegy V. New patients, Chapter 2. In: McDonald S, Excell L (eds). ANZDATA Registry Report 2005. Adelaide: Australia and New Zealand Dialysis and Transplant Registry, South Australia, pp. 33–43
8. Canadian Institute for Health Information. Canadian Organ Replacement Register Annual Report: Treatment of End-Stage Organ Failure in Canada, 2000 to 2009. Ottawa, Ontario, CIHI, 2011
9. Caskey FJ, Kramer A, Elliott RF et al. Global variation in renal replacement therapy for end-stage renal disease. Nephrol Dial Transplant 2011; 26: 2604–2610
10. U.S. Renal Data System. USRDS 2011 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2011
11. Croatian Registry of Renal Replacement Therapy. www.hdndt.org (date last accessed, 3 July 2012)
12. National Cancer Institute. Statistical Research and Applications Branch. Joinpoint Regression Program, Version 3.3, April 2008. http://srab.cancer.gov/joinpointual (Report)
13. Rosansky SJ, Clark WF, Eggers P et al. Initiation of dialysis at higher GFRs: is the apparent rising tide of early dialysis harmful or helpful? Kidney Int 2009; 76: 257–261
14. Cooper BA, Branley P, Bufone L et al. A Randomized, controlled trial of early versus late initiation of dialysis. N Engl J Med 2010; 363: 609–619
15. World Health Organization (WHO). World Health Statistics Annual. Geneva: WHO, 1955–1997. Since 1998 downloadable via Internet
16. Levi F, Chatenoud L, Bertuccio P et al. Mortality from cardiovascular and cerebrovascular diseases in Europe and other areas of the world: an update. Eur J Cardiovasc Prev Rehabil 2009; 16: 333–350
17. World Health Organization (WHO). Europe. European Health for All (HFA) Database. 2010. http://www.euro.who.int/en/what-we-do/data-and-evidence/databases/european-health-for-all-database-hfa-db2 (date last accessed, 3 July 2012)