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Gender disparities in mortality from infectious diseases in Serbia, 1991–2014: a time of civil wars and global crisis

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SUMMARY

Infectious diseases remain one of the leading causes of death worldwide. The aim of this descriptive epidemiological study was to analyse the trends in mortality from infectious diseases in Serbia (excluding the Autonomous Province of Kosovo & Metohia) from 1991 to 2014 using joinpoint regression analysis. The mortality rates from infectious diseases were found to have increased markedly from 1991 to 1994 (+12·4% per year), followed by a significant decline from 1994 to 2009 (–4·6% per year) and then another increase from 2009 to 2014 (+4·3% per year). Throughout the study period, mortality rates were consistently higher in men than in women. Although a substantial decline was observed for young people of both sexes, no consistent pattern was evident for the middle-aged nor the elderly. Since 1991, septicaemia has emerged as a leading cause of infectious disease mortality, particularly in older men. The Yugoslav civil wars in the 1990s and the global financial crisis in 2008 corresponded with changes in the trends in mortality from infectious diseases in Serbia, with the elderly showing particular vulnerability during those time periods. Data presented in this study might be useful to improve control of infectious diseases in Serbia.

Key words: Infectious diseases, joinpoint analysis, mortality, trend.

INTRODUCTION

Infectious diseases remain a significant public health problem [1–3]. According to the World Health Organization (WHO) estimates from 2012 [1], infectious diseases caused an estimated 6·4 million deaths worldwide (representing about 11·5% of all deaths), down from 8·7 million deaths (16·4% of the global death rate) in 2000. Infectious diseases were reported as the most common cause of death in low-income countries, accounting for nearly 2·1 million deaths each year and ~28·2% of all annual deaths in both sexes. In Europe, which encompasses countries with more advanced economies generally, deaths by infectious diseases accounted for only 2·5% of all deaths (an estimated 234 000 deaths). The majority (97·5%) of deaths from infectious diseases occurred in developing countries, and infectious diseases were ranked first among causes of death therein. Mortality of infectious diseases was highest in Sub-Saharan Africa (considered the most vulnerable region, with infectious diseases accounting for 34·5% of all deaths in 2012), while the lowest was recorded in the European region (2·6% of all deaths in 2012).

The rates of mortality from infectious diseases have shown a considerable decreasing trend throughout the 20th century for developed countries, such as the

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Statistical analysis

Three types of death rates were calculated: crude, specific (age- and sex-specific) and age-standardized (expressed per 100 000 persons). Age-specific mortality rates were calculated for all ages and within age groups (0–4, 5–19, 20–49, 50–64, ⩾65 years). Category standardization was performed by direct method, with 'European population' used as the standard population and age stratified by 5-year intervals.

Mortality trends from infectious diseases were assessed using joinpoint regression analysis (Joinpoint Regression Program, v. 4·0·4 – May 2013, available through the Surveillance Research Program of the US National Cancer Institute). The joinpoint analysis software detected occurrences of statistically significant changes (joinpoints) and determined the trends between joinpoints. Permutation tests were performed to identify the best-fitting combination of line segments and joinpoints [15]. The bivariables were sex and age group. The results are presented as straight lines connected at change points, on a log scale, and the trends in annual age-standardized mortality rates (ASRs) are characterized by an annual percentage change (APC) between successive change points. All estimates are presented with 95% confidence intervals (CIs) [16]. Disparities in mortality trends according to sex and age were tested by comparability testing [17], which determined whether the two regression mean functions were identical (test of coincidence) or parallel (test of parallelism). $P < 0·05$ was considered statistically significant for all tests.

Table 1. *Infectious diseases and overall mortality in Serbia, 1991–2014; specified infectious diseases as a proportion of all causes of deaths*

	Infectious diseases		% of all causes	All causes of deaths	
Year	No.	ASR	of deaths	No.	ASR
1991	484	6·0	0·54	89 072	1129·9
1992	550	6·7	0·59	93 475	1179·0
1993	610	7·9	0·64	95 121	1190·0
1994	648	8·1	0·70	93 011	1145·9
1995	614	7·7	0·65	93 933	1137·3
1996	725	8·7	0·74	98 370	1174·8
1997	618	7·3	0·63	98 068	1157·3
1998	576	6·7	0·58	99 376	1160·2
1999	565	6·4	0·56	101 444	1161·3
2000	577	6·7	0·55	104 042	1173·6
2001	512	5·8	0·52	99 008	1100·9
2002	540	5·9	0·53	102 785	1136·1
2003	559	6·1	0·54	1 03 946	1130·4
2004	516	5·6	0·49	104 320	1099·6
2005	546	5·9	0·51	106 771	1092·8
2006	450	4·7	0·44	102 884	1025·6
2007	435	4·5	0·42	102 805	998·9
2008	394	4·0	0·38	102 711	976·3
2009	412	4·2	0·40	104 000	970·6
2010	441	4·5	0·43	103 211	947·4
2011	438	4·4	0·43	102 935	929·7
2012	454	4·4	0·44	102 400	928·5
2013	583	5·4	0·58	100 300	894·5
2014	555	5·2	0·55	101 247	887·1
Overall	12 802	6·0	0·53	2 405 235	1072·0

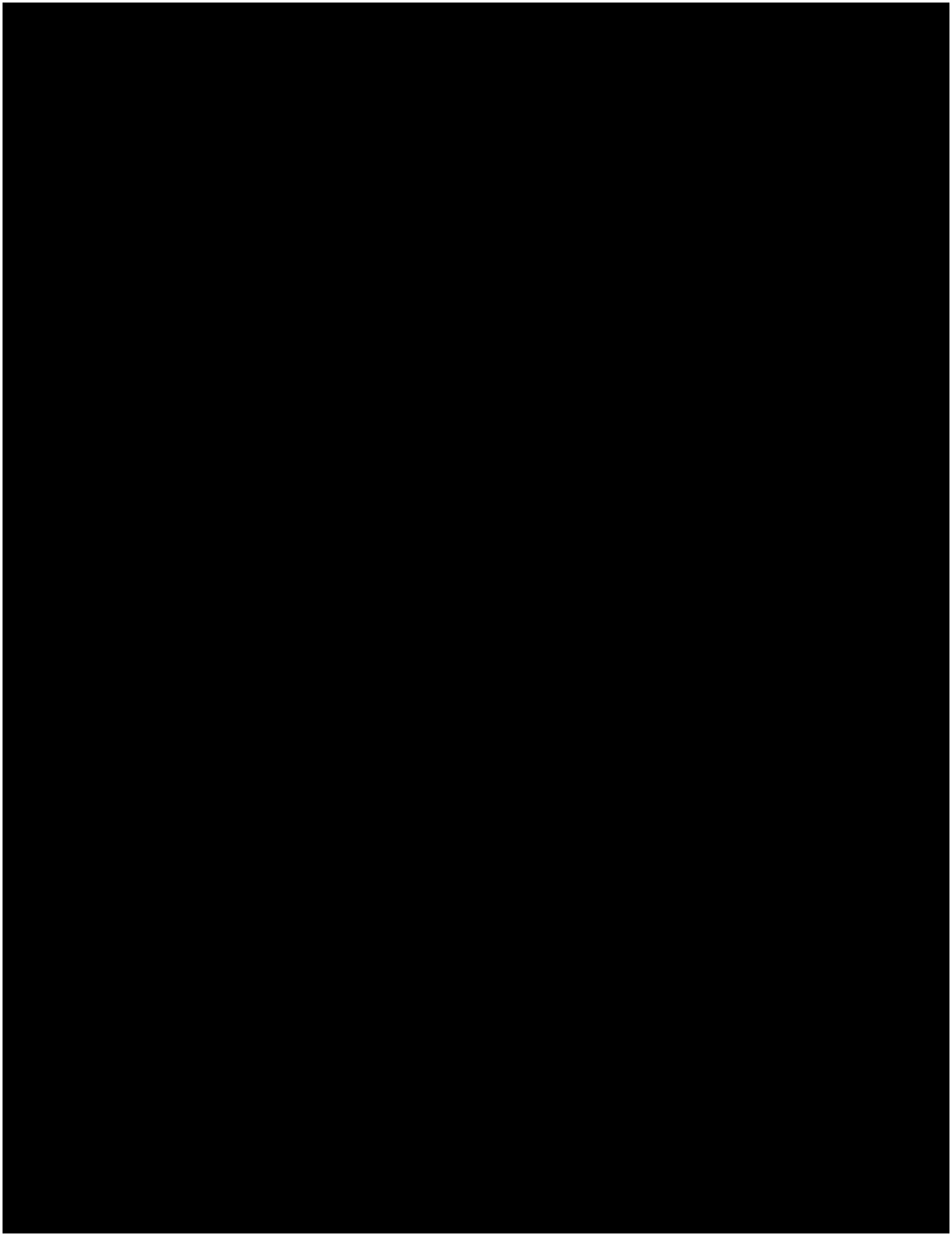
ASR, Age standardized rate (using European standard population, per 100 000).

RESULTS

Infectious diseases accounted for 0·5% of total deaths in Serbia during the study period. Nearly 13 000 (male to female ratio 1·6:1) infectious disease deaths were recorded, with the average annual ASR being 6·0/100 000 inhabitants (Table 1). The mortality rates from infectious diseases were twofold higher in men (8·2/100 000) than in women (4·1/100 000), and the average ASR for overall mortality was higher in men (1285·3/100 000) than in women (894·6/100 000).

The mortality rates from infectious diseases showed marked increases from 1991 to 1994 (+12·4% per year) and significant decreases from 1994 to 2009 (–4·6% per year) followed by renewed increases from 2009 to 2014 (+4·3% per year) (Fig. 1). However, the trend in overall mortality showed a significant decrease over the entire study period (–1·3% per year). For the overall analysis of 1991–2014 only one joinpoint was detected, representing a non-significant change, showing a small increase (+0·1% per year) from 1991 to 2000, followed by a significant decrease (–2·0% per year from 2000 onwards). The mortality trends from infectious diseases and overall mortality in Serbia differed significantly (i.e. the final selected model rejected parallelism, $P < 0·05$).

Men showed a non-significant increase for infectious disease mortality during the period 1991–1993, which was followed by a significant decrease from 1993 to 2005 (–2·8% per year), a non-significant decrease from 2005 to 2008, and a steady increase from 2008 onwards (+3·6% per year) (Fig. 2). The trend in overall mortality for men showed significant decrease over the entire study period (–1·3% per year); only one joinpoint was detected, representing a non-significant



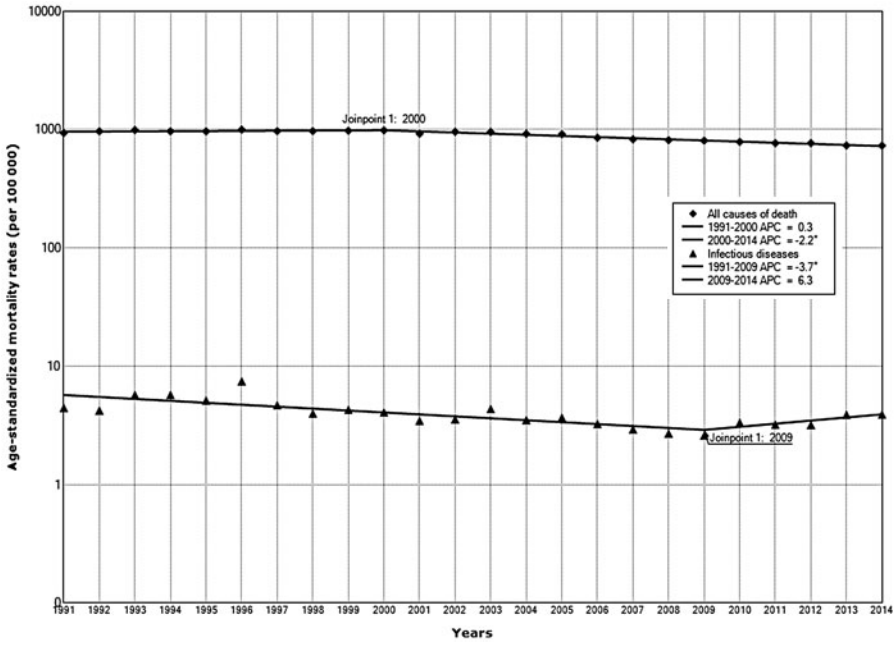


Fig. 3. Mortality from infectious diseases and overall mortality in women in Serbia, 1991–2014: a joinpoint regression analysis (using logarithmic scale). All causes of death (1 joinpoint) *vs.* infectious diseases (1 joinpoint). * Statistically significant trend; APC, annual percent change.

In women, infectious disease mortality decreased significantly from 1991 to 2009 (–3·7% per year), but then increased non-significantly from 2009 onwards (Fig. 3). The trend in overall mortality for women showed significant decrease over the entire study period (–1·3% per year); one joinpoint was detected, representing a non-significant change, with a small increase from 1991 to 2000 (+0·3% per year), followed by a significant decrease from 2000 onwards (–2·2% per year). The mortality trends from infectious diseases and overall mortality for women in Serbia differed significantly (i.e. the final selected model rejected parallelism, $P < 0{\cdot}05$).

When stratified by age group and sex, the rates of infectious disease mortality were higher in men than in women for all age groups (Table 2). Although there was a trend of substantial decline over time for young people of both sexes, no consistent pattern was evident for the middle aged and the elderly. In males aged 20–49 years, the mortality rates significantly increased from 1991 to 1998 (+7·4% per year), and then significantly decreased from 1998 to 2014 (–5·2% per year). In males aged 50–64 years, the mortality rates increased from 1991 to 2000 and then showed a significant decline until 2011 (–4·6% per year) followed by a sharp increase until 2014. In the oldest group of males ($\geqslant 65$ years), the mortality rates showed a non-significant increase from 1991 to 1996 that was followed by a significant decrease from 1996 to 2009 (–4·3% per year) followed by a rapid increase from 2009 onwards (+8·9% per year). In females aged 20–49 years, mortality increased non-significantly from 1991 to 1997, but then significantly and consistently decreased from 1997 onwards (–6·3% per year). Middle-aged females (50–64 years) showed a significant declining trend in mortality (–1·9% per year) over the entire study period, while elderly females ($\geqslant 65$ years) showed a stable trend over the entire study period. Comparability testing indicated that mortality trends from infectious diseases in men aged $\geqslant 20$ years differed significantly from trends in the other age groups (i.e. the final selected model rejected parallelism, $P < 0{\cdot}05$).

The most frequent causes of death in both sexes were tuberculosis and septicaemia, accounting for 72% of all infectious disease deaths (9204/12 802) (Table 3). The proportional contribution of intestinal infectious diseases, viral hepatitis and HIV to total infectious disease mortality were nearly equal, amounting to a total of ~20%.

Mortality trends from tuberculosis and septicaemia differed significantly. The trend of mortality from tuberculosis showed significant decrease over the entire study period (–6·4% per year), while the corresponding trend of mortality from septicaemia showed an overall non-significant slight decrease (–0·8% per year) (Fig 4). A significantly increasing trend was observed only for the

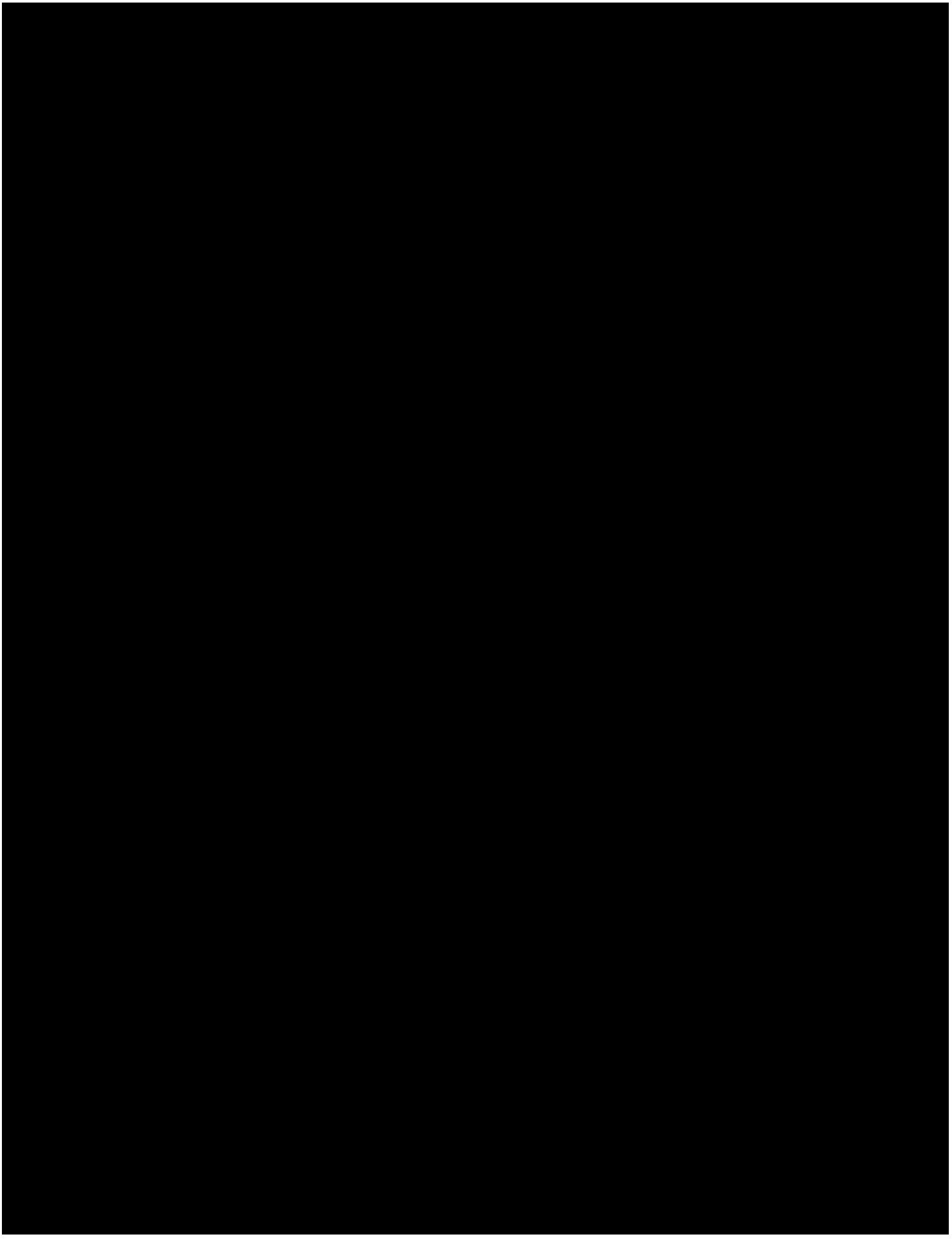


Table 3. *Infectious disease mortality in Serbia, 1991–2014; selected most common infectious diseases – number of deaths (age standardized rate, using European standard population, per 100 000)*

Year	Tuberculosis	Septicaemia	Intestinal infectious diseases	Viral hepatitis	HIV disease
1991	298 (3·5)	76 (1·0)	35 (0·6)	12 (0·1)	0 (0·0)
1992	365 (4·2)	73 (1·0)	30 (0·5)	16 (0·2)	2 (0·0)
1993	347 (4·0)	127 (1·8)	59 (1·0)	9 (0·1)	2 (0·0)
1994	366 (4·2)	164 (2·2)	50 (0·9)	15 (0·2)	1 (0·0)
1995	321 (3·6)	179 (2·4)	49 (0·9)	20 (0·2)	6 (0·1)
1996	334 (3·7)	242 (3·1)	45 (0·8)	16 (0·2)	11 (0·1)
1997	284 (3·1)	169 (2·1)	13 (0·2)	33 (0·4)	61 (0·8)
1998	279 (3·0)	171 (2·1)	16 (0·3)	11 (0·1)	56 (0·7)
1999	281 (3·1)	154 (1·8)	10 (0·2)	18 (0·2)	40 (0·5)
2000	281 (3·0)	146 (1·8)	18 (0·3)	18 (0·2)	41 (0·6)
2001	258 (2·7)	123 (1·5)	12 (0·2)	14 (0·2)	55 (0·7)
2002	264 (2·7)	159 (1·8)	7 (0·1)	24 (0·3)	30 (0·4)
2003	254 (2·7)	175 (1·8)	10 (0·2)	29 (0·3)	28 (0·4)
2004	230 (2·4)	176 (1·9)	6 (0·1)	27 (0·3)	26 (0·4)
2005	227 (2·7)	169 (1·9)	15 (0·2)	40 (0·4)	25 (0·3)
2006	184 (1·9)	120 (1·3)	9 (0·1)	52 (0·5)	25 (0·3)
2007	168 (1·7)	111 (1·1)	10 (0·1)	36 (0·4)	14 (0·2)
2008	137 (1·4)	116 (1·2)	21 (0·2)	50 (0·5)	16 (0·2)
2009	134 (1·3)	113 (1·1)	19 (0·2)	44 (0·5)	31 (0·4)
2010	137 (1·4)	148 (1·5)	33 (0·3)	44 (0·5)	34 (0·5)
2011	126 (1·2)	146 (1·4)	53 (0·5)	30 (0·3)	35 (0·5)
2012	128 (1·2)	148 (1·4)	72 (0·6)	42 (0·4)	23 (0·3)
2013	110 (1·1)	196 (1·8)	114 (0·9)	44 (0·4)	28 (0·4)
2014	87 (0·9)	203 (1·9)	136 (1·1)	41 (0·4)	12 (0·2)
Overall	5600 (2·5)	3604 (1·7)	842 (0·4)	685 (0·3)	602 (0·3)

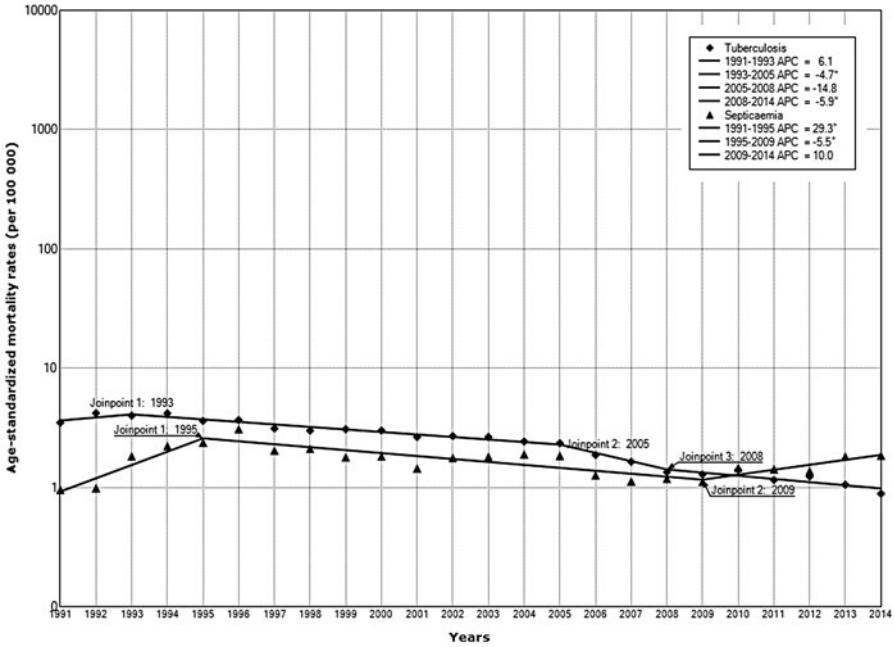


Fig. 4. Mortality from tuberculosis and septicaemia in Serbia, 1991–2014: a joinpoint regression analysis (using logarithmic scale). Tuberculosis (3 joinpoints) *vs.* septicaemia (2 joinpoints). * Statistically significant trend; APC, annual percent change.

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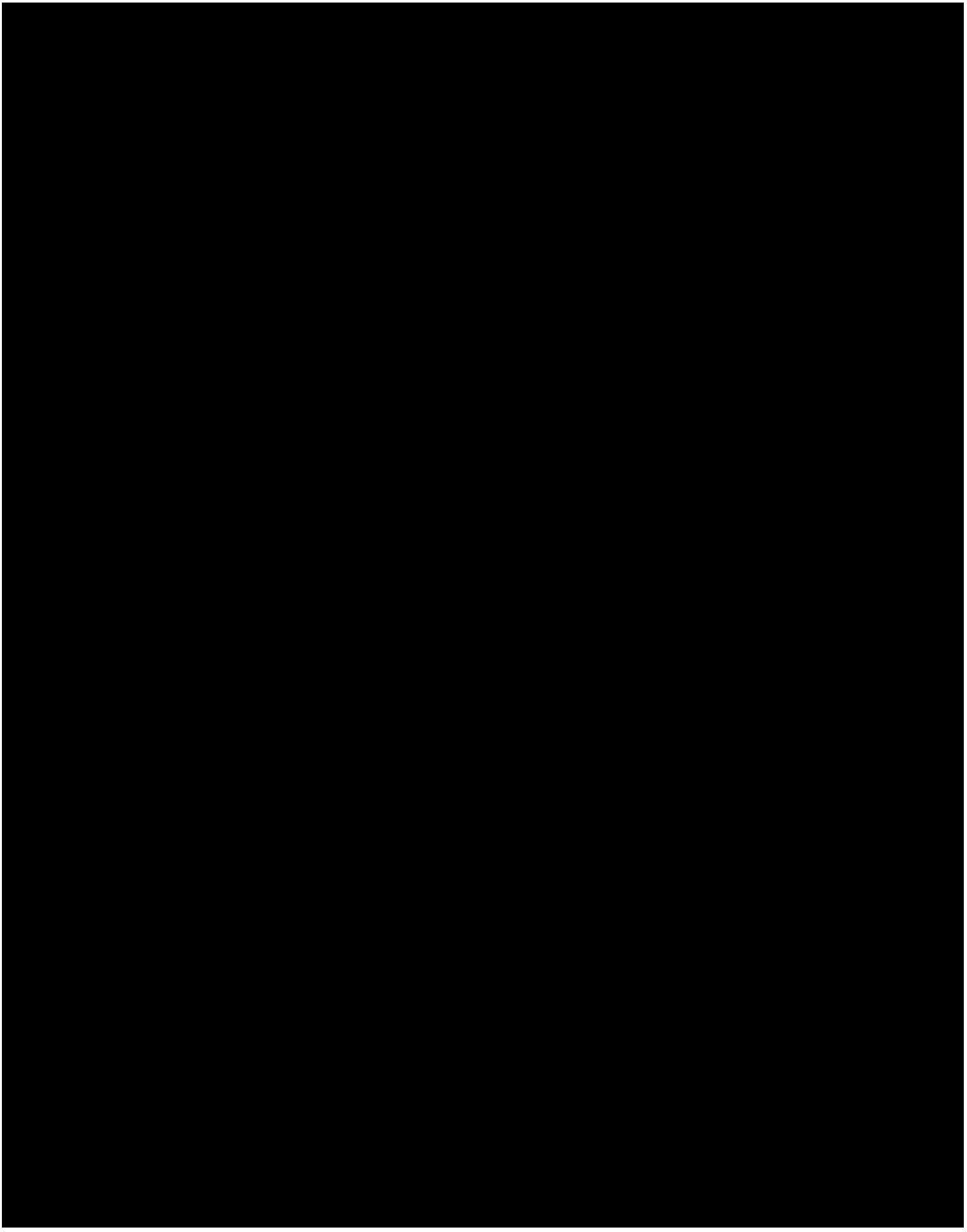
for these age and sex differences in mortality from infectious diseases remain unknown, but potential factors include socioeconomic, anatomical and behavioural aspects that may represent differences in exposure to pathogens, and biological aspects that may represent differences in susceptibility and response to infectious diseases (i.e. genetic and hormonal factors that may modulate immune responses against pathogens, susceptibility or disease progression, and responsiveness to treatment and vaccines) or that may lead to differences in resistance to severe infection [20, 21].

Unfavourable trends in mortality from infectious diseases in men in Serbia could be attributed primarily to mortality from septicaemia. The increased rates of deaths from septicaemia in Serbia might have been a consequence of unfavourable circumstances specific to the country's socio-political fluctuations during the observed period, namely the marked decline in the general standard of living, the unsatisfactory quality of health services (including a lack of vaccines, drugs, medical equipment, a large increase in wounded nationals and refugees requiring medical and social care, decreasing hospitalization rates, particularly for people aged $\geqslant$60 years, and irresponsible antibiotic use), social disintegration, ageing of the population that accompanies immunodeficiency, as well as other factors [19]. The relatively favourable trend in mortality from tuberculosis, on the other hand, may be attributed to the implementation of mass preventive programmes and improvements in tuberculosis treatment in Serbia [14].

An obvious declining trend was observed for overall mortality in Serbia during the entire study period (1991–2014), but stratification analysis by age and sex revealed different patterns within the trend of infectious disease mortality. A significant increasing trend in mortality from infectious diseases was observed in men aged 20–49 years during 1991–1998 and men aged $\geqslant$65 years (the oldest group) during 2009–2014. A decline in mortality from tuberculosis was observed in all age groups for both sexes, unlike the increasing trend in mortality from septicaemia that occurred in the last decade of the 20th century in all age groups in men and in women aged >50 years. Two joinpoints were noticed for men only: in 1995 when a significant increasing trend in septicaemia mortality was followed by a significant decrease, and in 2008 when a significant decreasing trend in septicaemia mortality was followed by a significant increase. For women, the mortality trend for septicaemia showed no significant changes over the entire study period. Significant changes in temporal trends of infectious disease mortality, especially for men, did not correspond to the temporal trends found for overall mortality in Serbia; this apparent discrepancy could be explained, at least partly, by the presence of a small percentage of infectious diseases in overall mortality and domination of non-communicable diseases, which themselves have shown an increasing trend in the observed period [22–24]. Of course, this increased mortality trend for infectious diseases could be merely a coincidence, although it can be surmised rather that the change in frequency of infectious diseases would be expected to occur within such a short period of time, unlike that for chronic non-communicable diseases, which are characterized by a significantly longer duration of pathogenesis. In times of crisis and wars, increasing trends in infectious diseases are commonplace and have been reported for many countries [25–31]. While the favourable mortality trend that was found in our study for tuberculosis corresponds to the implementation of preventive measures and therapy procedures [32], similar country-wide strategies for the prevention and treatment of septicaemia were very limited [19, 33]. According to our results, it can be concluded that the change in mortality trend from infectious diseases was caused by changes in mortality in men aged >20 years, most likely due to septicaemia.

Greater responsibility and stress may be placed on men in times of wars and economic crisis and this could be an explanation for the more unfavourable mortality from infectious diseases found in men than in women in Serbia [34, 35]. The period in which Serbia was subject to civil wars and United Nations sanctions (1992–1995) was followed by years marked by the collapse of the economy, deterioration of living conditions, brutal hyperinflation of the national currency, and collapse of the healthcare system, which included lack of medicines, vaccines and medical supplies [19, 33].

In the last decade of the 20th century, the former Yugoslavia was the scene of several wars that produced their own contingents of refugees that came to Serbia. Over the last 25 years, ~650 000 refugees have traversed from the former Yugoslavia to reside in Serbia [14, 36]. Over the past two decades, ~140 000 of these refugees have returned to their countries of origin and ~50 000 persons migrated to third countries; however, the majority of the refugees have remained in Serbia and integrated into the social and economic fabric of the country. Additionally, nearly 300 000 of the internally



DECLARATION OF INTEREST

The authors have no conflicts of interests to declare in relation to this study or publication of its findings.

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