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AN OVERVIEW OF TRENDS IN INFECTIOUS DISEASE MORTALITY, TURKEY: 2009-2018

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ABSTRACT

Objective: *Infectious diseases continue to be one of the leading causes of death worldwide. This descriptive epidemiological study aimed to evaluate the trends in mortality from infectious diseases in Turkey from 2009 to 2018 using joinpoint regression analysis.*

Material and Method: *Mortality data used in this study, which belong to the years 2009-2018, were obtained from the Turkey National Institute of Statistics records. Age-standardized mortality rates were calculated using a direct method by the age group of the proposed world population. To identify significant changes in trends, joinpoint regression analysis was performed.*

Results: *During the study period, about 168,000 people died from infectious diseases. The age-standardized mortality rate from the infectious disease increased from 9.82/100,000 in 2009 to 29.07/100,000 in 2018. Throughout the study period, mortality rates were consistently higher in males than in the female. During the period, the greatest significant increase in both males (23.2% per year) and females (23.1% per year) was in pneumonia.*

The results showed that pneumonia mortality was of great importance for elderly patients.

Conclusion: *To reduce the mortality rates associated with infection, protective measures should be taken in the elderly and, pneumonia and sepsis disease should be the focus of preventive policies in the elderly population.*

Keywords: *Infectious diseases, mortality, joinpoint regression analysis.*

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ENFEKSİYÖZ HASTALIK MORTALİTELERİNDEKİ TRENDLERE GENEL BİR BAKIŞ, TÜRKİYE: 2009-2018

ÖZET

Amaç: Enfeksiyon hastalıkları, dünya çapında önde gelen ölüm nedenlerinden biri olmaya devam etmektedir. Bu tanımlayıcı epidemiyolojik çalışmanın amacı 2009-2018 yılları arasında Türkiye'de enfeksiyon hastalıkları mortalite oranlarındaki trendleri joinpoint regresyon analizi ile değerlendirmektir.

Materyal ve Metot: Bu çalışmada kullanılan 2009-2018 yıllarına ait mortalite verileri Türkiye Ulusal İstatistik Enstitüsü kayıtlarından elde edildi. Yaşa göre düzeltilmiş mortalite oranları, önerilen dünya nüfusunun yaş dağılımına göre doğrudan düzeltme yöntemi kullanılarak hesaplandı. Trendlerdeki önemli değişiklikleri belirlemek için joinpoint regresyon analizi uygulandı.

Bulgular: Çalışma periyodu boyunca yaklaşık 168.000 kişi enfeksiyon hastalıklardan öldü. Enfeksiyon hastalıklarında yaşa göre düzeltilmiş mortalite oranı 2009'da 9,82/100.000'den 2018'de 29,07/100.000'e yükselmiştir. Çalışma süresi boyunca mortalite erkeklerde kadınlara göre daha yüksekti. Dönem boyunca hem erkek (her yıl %23,2) hem de kadınlarda (her yıl %23,1) en büyük anlamlı artış pnömonide olmuştur.

Sonuçlar pnömoni mortalitesinin yaşlı hastalar için büyük önem taşıdığını göstermiştir.

Sonuç: Enfeksiyonla ilişkili mortalite oranlarını azaltmak için yaşlılarda koruyucu önlemler alınmalı ve yaşlı nüfusta pnömoni ve sepsis hastalığı önleyici politikaların odağı olmalıdır.

Anahtar kelimeler: Enfeksiyon hastalıkları, mortalite, joinpoint regresyon analizi.

INTRODUCTION

Despite a century of successful prevention and control efforts, the global burden of infectious diseases remains a major global problem in public health.[1] Infectious disease today ignores the geographic and political boundaries and therefore constitutes a global threat that puts every nation and every person at risk. Infectious diseases continue to be a burden on populations around the world. Biological threats, both naturally occurring and deliberate, have the potential to cause disease, disability, and death.[2]

Infectious diseases continue to be the leading causes of ill health among poor people.[3] These diseases kill about 9 million people each year. Most of these deaths were poor people in low- and middle-income countries, and most deaths occurred in children under the age of five. Infectious diseases are prevalent among those affected by conflict and populations living in war zones, internally displaced populations, refugees.[4]

The joinpoint regression (JR) model defines significant changes in the incidence, mortality, and survival trends of a specific disease in a given population. JR is widely applied to detect these change points and determine the trends between joinpoints. Having good estimates and predictions of such mortality rates helps us not only to monitor and evaluate the current status of the disease but also to establish an evidence-based policy for resource allocation. Thus, the main objectives of the present study are as follows (a) to determine significant increases or decreases in infectious diseases' mortality (b) to describe the mortality rate according to the age distribution in males and females.

MATERIAL AND METHOD

Data Collection

Infectious disease mortality data for the years 2009 to 2018, which reported from the Turkish Statistical Institute death database was used.[5] Results are presented for the following infectious disease types as defined by International Classification of Diseases, 10th revision (ICD-10). We analyzed trends by age group (<4 years, 5-14 years, 15-64 years, and 65 years and over) and infectious disease [intestinal infections (A00-A09), tuberculo sis (A15-A19, B90), sepsis (A40-A41), HIV-related disease (B20-B24), pneumonia (J12-J18), viral hepatitis (B15-B19), influenza (J09-J11), acute respiratory(J00-J08), meningitis (G00-G03) and meningococcal infections (A39)].

All analyzes were performed separately for both genders. Age-standardized death rates per 100,000 population (using WHO standard population) were computed for each year using direct standardization.[6]

The age-standardized rate is the weighted average of the age-specific rates; where weights are the proportions of the population in the suitable age groups of a standard population. The age-standardized rate for an age group comprised of the ages x through y is computed using the following formula:

$$\text{Age-standardized rate}_{x\text{-}y} = \sum_{i=x}^{y} \left[\left(\frac{count_i}{pop_i} \right) x100{,}000 x \left[\frac{stdpop_i}{\sum_{j=x}^{y} stdpop_j} \right] \right]$$

For the standardization, five-year age groups were used. The present approach adjusts crude rates by the age distribution, therefore it is useful for comparing populations of dissimilar countries.

Statistical Analysis

In epidemiological studies, JR analysis is widely used in modeling trends in mortality or incidence series. The analysis begins with the minimum number of joinpoints and tests whether one or more joinpoints are statistically significant and should be added to the model. The number of joinpoints is determined by performing permutation tests (A permutation test calculates the probability of values equal to or greater than the observed values of the test statistic under the determined null hypothesis by recalculating the test statistics after random reordering of the data), each of which had a correct asymptotic significance level. This level of significance is found using Monte Carlo methods and applying Bonferroni corrections.[7] The final model shows the best fitting joinpoints where the rate changes significantly. Each joinpoint informs of a statistically significant change, an estimated annual percent change (APC), and average annual percent change (AAPC) that are calculated with 95% confidence intervals (95%CI). AAPC is the geometric mean of the annual changes from all of the partitions.[8,9] It is the same for APC and AAPC zero joinpoints. When describing trends, the terms "increase" and "decrease" are used when the slope of the trend (positive APC or AAPC; negative APC or AAPC) is statistically significant. Changes in mortality rates over time were analyzed according to the equation (APC=[exp(β)-1]x100), where β is the slope of the regression of log rates over one year. In this study, infectious disease rates were specified per 100,000 people per year.[7] Analyzes were applied using the Joinpoint Regression Program 4.7.0.0–2018 offered by the surveillance research program of The USA National Cancer Institute.[10] The average annual percentage changes for mortality rates were described with a 95% confidence interval. Since our study includes 9 years, we let the maximum number of joinpoints for analysis as one (As the recommended maximum number of joinpoints is in the range of 7-11).[11] Analyzes were applied at a 0.05 significance level.

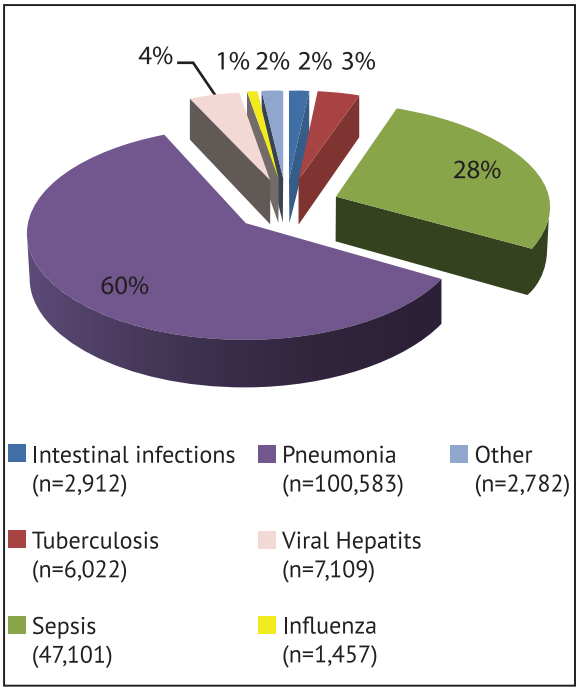

Figure 1. Distribution of common infectious disease mortality in Turkey, 2009 to 2018

RESULTS

Between the years 2009-2018 stems from a total of 3.615 million people who had lost their lives in Turkey, of which approximately 4.6% of infectious diseases (about 168,000 people). While the rate of deaths of infectious diseases in total deaths was 2.6 in 2009, this rate increased to 7.7 in 2018. So it has increased about 3 times. Most of those who died from infectious diseases were pneumonia (more than 100,000 deaths, nearly 60% of all) (Figure 1). Also, approximately 88% of deaths in infectious diseases are pneumonia and sepsis.

The age-standardized mortality rate (ASR) from infectious diseases increased from 9.82/100,000 population in 2009 to 29.07/100,000 population in 2018. The ASR from infectious diseases has increased since 2009, from 11.64 per100,000 to 34.68 per 100,000 for males and from 8.26 per 100,000 to 24.45 per 100,000 for females in 2018 (Table 1). Pneumonia was the leading cause of infectious disease death both in 2009 and 2018 in both genders (male:4.19/100,000 population in 2009 and 23.06/100,000 population in 2018; female: 2.98/100,000 population in 2009 and 14.05/100,000 population in 2018). Of the top 5 infectious diseases, acute respiratory infections (on the 2009 list) were replaced by intestinal infections in males (on the 2018 list). In females, of the top 5 infectious diseases, tuberculosis, ranked 4th in 2009, fell to 5th in 2018, with non-listed intestinal infections rising to 4th place (Table 2).

The results of the JR, the APC for each trend, and the AAPC for males and females are shown in Table 3.JR analysis results indicated that there was an overall significant trend for mortality of infectious diseases in Turkey over the entire observation period (AAPC=+15.3%, 95% CI 12.9;17.7) (Figure 2).

When evaluated according to sepsis and pneumonia, the zero joinpoint model was found to be the best-fit model for both genders. During the period, a significant increase in the mortality rate of pneumonia and sepsis was observed in both sexes. Throughout the study period, there was a significant increase in HIV-related disease in men, while there was an increase in women, but it was not significant. JR showed that both viral hepatitis and tuberculosis mortality decreased similarly both in males and females. Significant decreases in viral hepatitis and tuberculosis mortality rate were observed in both sexes, especially after 2013. As a result, AAPCs of acute respiratory mortality for the full period in males and females were–27.2% (95% CI–39.8 to–3.9) and –28.2% (95% CI–39.3 to–15.1), respectively. The age-standardized intestinal infectious mortality rate for males showed a significant 72.3% increase each year from 2009 to 2013 and a significant decrease of-11.6% from 2013 to the end of the period. A similar situation was valid in females (a significant increase of 68.5% per year from 2009 to 2013, and a significant decline of–11.7% per year from 2013 onwards). A steady increase was observed in influenza mortality during the period (2009-2018) in males but non-significant. The female, influenza mortality non-significantly increased by 3.3 percent per year from 2009 to 2018 (p=0.60).

The results of the JR analysis by age group for sepsis and pneumonia disease mortality are summarised in Table 4. In sepsis disease, among the 0-4 age group, 2 periods of change were evident. The first period (2009-2013) was associated with an APC of –11.1 (p<0.001) and the second period (2013-2018) with an APC of 2.0 (p=0.20). Overall, the average APC for 2009-2018 was–4.0, reflecting a significant decrease from 5.75 to 3.62 deaths/100,000 population. Among the people in the 5-24 age group, the average APC increased during 2009–2018 (AAPC= 5.1) but non-significant (p=0.10). The most obvious increases in mortality were in people with 25 and over age group during 2009–2018 (AAPC=8.3 for 25-44; AAPC=10.8 for 45-64; AAPC=16.9 for 65-and over; p<0.001).

During the working period, a steady significant increase was observed in pneumonia disease mortality for 5 and over age groups. The highest significant increase was realized in 45 and over (AAPC=25.3 for 45-64 age group; AAPC=29.6 for 65 and over age group). Although no significant decrease was observed in the 0-4 age groups during the years of 2009-2011, significant increases were observed from 2011 to the end of the period (APC:9.7; CI: 1.3 to 18.6).

Table 1. Deaths, Crude rates and age-standardised mortality rates from infectious disease by sex, Turkey, 2009-2018.

	Male			Female			Overall		
Years	**Deaths**	**Crude rate**	**ASR**	**Deaths**	**Crude rate**	**ASR**	**Deaths**	**Crude rate**	**ASR**
2009	3395	10.96	11.64	3327	9.22	8.26	7322	10.09	9.82
2010	4065	10.97	11.44	3499	9.54	7.92	7564	10.26	9.55
2011	4791	12.76	12.92	4154	11.17	8.87	8945	11.97	10.73
2012	4915	12.95	12.75	4456	11.83	9.12	9371	12.39	10.77
2013	6743	17.53	16.90	5852	15.32	11.48	12595	16.43	13.94
2014	8382	21.50	20.13	7673	19.82	13.94	16055	20.66	16.78
2015	10584	26.79	24.30	9963	24.40	17.39	20547	26.09	20.52
2016	12914	32.25	28.76	12229	30.75	20.69	25143	31.50	24.35
2017	14426	35.59	31.13	13832	34.34	22.18	28258	34.97	26.25
2018	16698	40.59	34.68	15778	38.61	24.45	32476	39.60	29.07

ASR: Age-standardised rate

Table 2. Causes of death from major infectious disease, 2009 and 2018

	2009		Male	2018	
	Deaths	**ASR**		**Deaths**	**ASR**
Pneumonia	1,461	4.19	Pneumonia	9,504	23.06
Sepsis	1,173	3.52	Sepsis	3,857	9.55
Tuberculosis	552	1.57	Tuberculosis	336	0.62
Viral Hepatits	408	1.19	Viral Hepatits	313	0.51
Acute respiratory	175	0.51	Intestinal infections	145	0.29
Pneumonia	1,268	2.98	Pneumonia	9,078	14.05
Sepsis	1,080	2.76	Sepsis	3,985	7.44
Viral Hepatits	315	0.81	Viral Hepatits	246	0.31
Tuberculosis	253	0.61	Intestinal infections	200	0.28
Acute respiratory	192	0.51	Tuberculosis	132	0.24

ASR: Age-standardised rate

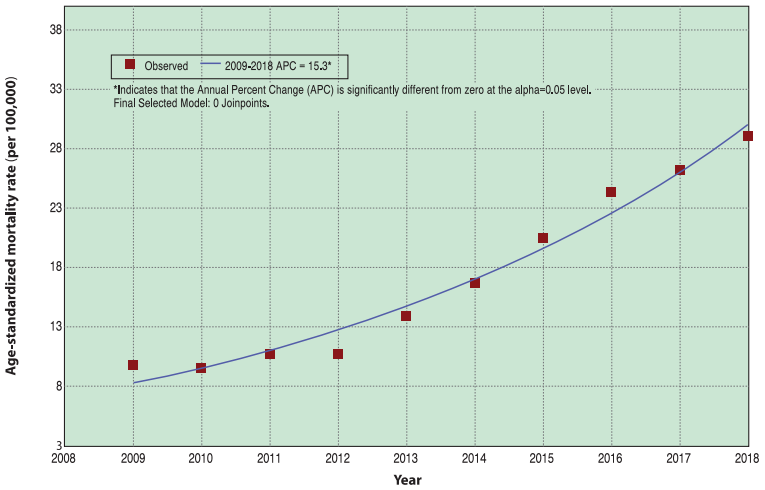

Figure 2. Age-standardizedinfectious diseases mortality trend in Turkey, 2009-2018; joinpoint regression analysis

Table 3. Trends in age-standardized death rates for infectious disease in Turkey according to joinpoint regression analysis, 2009–2018 (Male, Female)*

	AAPC(95% CI) Full Range (2009-2018)	Trend 1		Trend 2	
		Period	APC (95% CI)	Period	APC (95% CI)
Male					
Pneumonia	22.8 ^ (19.0 to 26.7)	2009-2018	22.8 ^ (19.0 to 26.7)	-	-
Sepsis	13.0 ^ (10.5 to 15.6)	2009-2018	13.0 ^ (10.5 to 15.6)	-	-
Viral Hepatits	-7.9 ^ (-10.9 to -4.8)	2009-2013	3.7 (-3.2 to 11.1)	2013-2018	-16.3 ^ (-20.7 to -11.6)
Tuberculosis	-9.2 ^ (-10.2 to -8.1)	2009-2018	-9.2 ^ (-10.2 to -8.1)	-	-
Intestinal infections	18.9 ^ (7.1 to 32.1)	2009-2013	72.3 ^ (30.1 to 128.3)	2013-2018	-11.6 ^ (-20.4 to -1.8)
Meningitis	0.2 (-2.7 to 3.2)	2009-2018	0.2 (-2.7 to 3.2)	-	-
Influenza	7.6 (-7.3 to 25.0)	2009-2018	7.6 (-7.3 to 25.0)	-	-
HIV-related disease	6.9 ^ (3.3 to 10.6)	2009-2018	6.9 ^ (3.3 to 10.6)	-	-
Acute respiratory	-27.2 ^ (-39.8 to -3.9)	2009-2018	-27.2 ^ (-39.8 to -3.9)	-	-
Meningococcal infections	-2.6 (-9.3 to 4.6)	2009-2018	-2.6 (-9.3 to 4.6)	-	-
Female					
Pneumonia	22.6 ^ (18.3 to 26.9)	2009-2018	22.6 ^ (18.3 to 26.9)	-	-
Sepsis	12.8 ^ (10.3 to 15.3)	2009-2018	12.8 ^ (10.3 to 15.3)	-	-
Viral Hepatits	-8.5 ^ (-12.6 to -4.1)	2009-2013	0.6 (-8.7 to 10.9)	2013-2018	-15.1 ^ (-21.5 to -8.3)
Tuberculosis	-7.8 ^ (-10.4 to -5.1)	2009-2018	-7.8 ^ (-10.4 to -5.1)	-	-
Intestinal infections	17.6 ^ (5.0 to 31.8)	2009-2013	68.5 ^ (24.6 to 127.9)	2013-2018	-11.7 ^ (-21. to -0.7)
Meningitis	-1.4 (-5.4 to 2.8)	2009-2018	-1.4 (-5.4 to 2.8)	-	-
Influenza	3.3 (-10.7 to 19.5)	2009-2018	3.3 (-10.7 to 19.5)	-	-
HIV-related disease	9.0 (-0.6 to 19.6)	2009-2018	9.0 (-0.6 to 19.6)	-	-
Acute respiratory	-28.2 ^ (-39.3 to -15.1)	2009-2018	-28.2 ^ (-39.3 to -15.1)	-	-
Meningococcal infections	4.3 (-5.3 to 15.2)	2009-2018	4.3 (-5.3 to 15.2)	-	-

***AAPC:** Average Annual Percent Change; **CI:** Confidence Interval; **APC:** Annual Percent Change; **^:** APC and AAPC are statistically significantly different from zero (two-sided $p < 0.05$); selection of the model: permutation test with 4,499 replications.

Table 4. Trends in age-specific crude rate mortality rates associated with sepsis and pneumonia disease derived using joinpoint regression analysis, (2009-2018)*

Age-Groups	Crude mortality rate		AAPC(95% CI) Full Range (2009-2017)	Trend 1		Trend 2	
	2009	2018		Period	APC (95% CI)	Period	APC (95% CI)
Sepsis							
0-4	5.75	3.62	-4.0 ^ (-6.1 to -1.9)	2009-2013	-11.1 ^ (-15.1 to -6.9)	2013-2018	2.0 (-1.5 to 5.7)
5-24	0.24	0.44	5.1 (-1.4 to 12.1)	2009-2018	5.1 (-1.4 to 12.1)	-	-
25-44	0.58	1.07	8.3 ^ (3.7 to 13.1)	2009-2018	8.3 ^ (3.7 to 13.1)	-	-
45-64	3.77	9.15	10.8 ^ (8.5 to 13.2)	2009-2012	-2.4 (-9.5 to 5.3)	2012-2018	18.1 ^ (15.9 to 20.2)
65 and over	23.55	96.30	16.9 ^ (14.6 to 19.3)	2009-2018	16.9 ^ (14.6 to 19.3)		-
Pneumonia							
0-4	5.17	6.17	3.0 (-8.0 to 15.4)	2009-2011	-17.2 (-55.0 to 52.2)	2011-2018	9.7 ^ (1.3 to 18.6)
5-24	1.79	3.67	10.9 ^ (7.0 to 15.0)	2009-2018	10.9 ^ (7.0 to 15.0)	-	-
25-44	2.68	6.49	16.7 ^ (8.7 to 25.3)	2009-2018	16.7 ^ (8.7 to 25.3)	-	-
45-64	6.12	38.75	25.3 ^ (20.2 to 30.6)	2009-2018	25.3 ^ (20.2 to 30.6)	-	-
65 and over	28.58	279.58	29.6 ^ (24.9 to 34.5)	2009-2016	34.3 ^ (28.6 to 40.2)	2016-2018	14.4 (-2.4 to 34.0)

***AAPC:** Average Annual Percent Change; **CI:** Confidence Interval; **APC:** Annual Percent Change; **^:** APC and AAPC are statistically significantly different from zero (two-sided $p < 0.05$).

DISCUSSION

Analyzing temporal trends in infectious disease mortality in Turkey is important to let comparison of data at an international level to evaluate the impact of public health measures, and support the practice of future interventions and attempts. This is the first epidemiological study of infectious disease trends in Turkey that is determined using joinpoint regression analysis. Also, this study is the most recent analysis of the mortality of infectious diseases in Turkey. During the last ten years, the most important causes of infectious deaths are pneumonia and sepsis (Table 2). Especially mortality rates due to pneumonia and sepsis in elderly patients increased over the study period. According to this result, it is seen that urgent precautions should be taken for the prevention of pneumonia and sepsis in the elderly population in Turkey. Nevertheless, the data evaluated in this study were not separated into nosocomial and community-acquired (CA) as for these two disorders. This is one of the most important limitations of the study and it makes the interpretation difficult. But for elderly not only community-acquired but also nosocomial pneumonia and sepsis is a proven risk factor.[12-15] As in many countries in the world, in Turkey, there is an increasing trend in multidrug-resistant gram-negative bacilli that cause nosocomial pneumonia and sepsis. One of the major reasons for the development of antibiotic resistance in microorganisms is the inappropriate use of antibiotics.[16-18] So the most important measure to reduce the mortality nationally antibiotic use policies should be determined. Also, practices for the prevention of CA pneumonia and sepsis will contribute to the reduction of mortality in elderly patients. Control of comorbidities and vaccination programs are essential measures that should be taken additionally.[15] There is an increase in the rate of influenza-related death, which is not significant. This may be due to changing vaccine policy in Turkey. In people aged at least 65 years, the influenza vaccination ratio is 15.8% among males and 13.0% among females in 2013.[18] In 2011 "influenza platform (GPL)" was established in Turkey with the support from European Scientists Working on Influenza (ESWI). This platform contains many doctors from distinct disciplines. Working together, GPL and the National Ministry of Health develop many strategies to increase vaccination rates for example training family physicians, giving true information is disseminated to the public instead of misconceptions, free vaccine supply, etc.[19] As a result of all these continuous work influenza mortality may be decreased. Another infectious disease in which mortality rates have fallen is viral hepatitis. New development treatment options for hepatitis C and increased hepatitis B vaccination practices can be the reason for this event. With the new drugs introduced in 2016, a cure for chronic hepatitis c is provided.[20] The most striking result obtained in this study is that pneumonia and sepsis mortality rates increased significantly in all age groups except the 0-4 age group (Table 3). According to these results, patients over 45 are more likely to have deaths. On the other hand, it has been reported in the literature that pneumonia mortality is gradually decreasing in European countries.[21] Therefore, disease prevention efforts should focus on taking measures to reduce infections, especially in elderly patients in our country. In the 0-4 age group, significant reductions were observed between 2009-2013 for sepsis and between 2009-2011 for pneumonia. Decreases in mortality of selected infectious diseases may be due to improvement in medical facilities, the advancement of Science and Technology, which is the awareness of the infectious disease for people.

CONCLUSION

Following the infectious disease deaths data can help assess disease control and prevention. The trends defined the continued vulnerability of Turkey residents to infectious diseases. To reduce the mortality rates associated with infection, protective measures should be taken for the elderly, and influenza, pneumonia, and sepsis should be the focus of preventive policies in the elderly population.

*The authors declare that there are no conflicts of interest.

REFERENCES

1. Cohen ML. Changing patterns of infectious disease. Nature 2000; 406: 762–767.
2. Institute of Medicine. Informing the Future: Critical Issues in Health.2nd ed. Washington, DC: The National Academies Press; 2003.
3. Bhutta ZA, Sommerfeld J, Lassi ZS, Salam RA, Das JK. Global burden, distribution, and interventions for infectious diseases of poverty. Infect Dis Poverty 2014; 3: 21.
4. Global report for research on infectious diseases of poverty. World Health Organization on behalf of the Special Programme for Research and Training in Tropical Diseases, Switzerland 2012.
5. Turkish Statistical Institute (TurkStat). January 11, 2018. www.turkstat.gov.tr.
6. Ahmad OB, Boschi-Pinto C, Lopez AD, et al. Age standardization of rates: a new WHO standard. GPE Discussion Paper Series: No:31, 2001. World Health Organization.

7. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000; 19: 335–351.

8. Clegg LX, Hankey BF, Tiwari R, Feuer EJ, Edwards BK. Estimating average annual percent change in trend analysis. Stat Med 2009; 28: 3670–3682.

9. Kim H-J, Luo J, Chen HS, et al. Improved Confidence Interval for Average Annual Percent Change in Trend Analysis. Stat Med 2017; 36: 3059-3074.

10. Joinpoint Regression Program. Version 4.6.0.0; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute. May 1, 2018. https://surveillance.cancer.gov/joinpoint/

11. Joinpoint Regression Program Help Manual. Version 4.6.0.0, Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute. 2018. May 5, 2018. https://surveillance.cancer.gov/joinpoint/Joinpoint_Help_4.6.0.0.pdf.

12. Blot S, Koulenti D, Dimopoulos G, et al. Prevalence, risk factors, and mortality for ventilator-associated pneumonia in middle-aged, old and very old critically ill patients. Crit Care Med 2014; 42: 601-609.

13. Holter JC, Ueland T, Jenum PA, et al. Risk factors for long-term mortality after hospitalization for community-acquired pneumonia: a 5-year prospective follow-up study. PLoS One 2016; 11: e0148741.

14. Girard TD, Opal SM, Ely EW. Insights into severe sepsis in older patients: from epidemiology to evidence-based management. Clin Infect Dis 2005; 40: 719-727.

15. Liang SY, Mackowiak PA. Infections in elderly. Clin Geriatr Med 2007; 23: 441-456.

16. Demirturk N, Demirdal T. Causative agents of nosocomial bloodstream infections and their antimicrobial susceptibility patterns.Southeast Asian J Trop Med Public Health 2013; 44:1036-1042.

17. Theuretzbacher U. Global antimicrobial resistance in Gram-negative pathogens and clinical need. Curr Opin Microbiol 2017; 39: 106-112.

18. Akan H, Yavuz E, Yayla ME, et al. Factors affecting uptake to influenza vaccination among family physicians. Vaccine 2016; 34: 171-178.

19. Ciblak MA. Grip platformu Vaccine 2013; 31: 518-523.

20. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C. J Hepatol 2018; 69: 461-511.

21. Marshall DC, Goodson RJ, Xu Y, et al. Trends in mortality from pneumonia in the Europe union: a temporal analysis of the European detailed mortality database between 2001 and 2014. Resp Res 2018; 19: 81.