PUBLIC HEALTH

ASSESSMENT OF THE BURDEN OF SALMONELLOSIS IN THE REPUBLIC OF NORTH MACEDONIA

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Abstract

Food-related diseases still cause a significant public health, economic and social burden worldwide. Each year, 1 in 10 people become ill from food contaminated with microbes or chemical agents, resulting in 600 million illnesses, 420,000 deaths and loss of 33 million healthy life years globally. The aim of this study was to determine the burden of infections caused by Salmonella spp. at national level, and to determine the public health and economic impact. Material and methods: Data from the National database of infectious diseases for 2019 were used; incidence, years of life lost (YLL), years lost due to disability (YLD), disability-adjusted life years (DALY) and economic losses were determined. Results: The analysis included 197 salmonellosis patients, of which 101 or 51.3% were male patients and 96 or 48.7% were female patients. The largest number of cases occurred in month XI (November) with 46 cases. The most represented age group were children aged 0-5 years (79 patients). The largest number of cases were registered in Skopje - 80 cases (40.6%). Data analysis showed a significant association between clinically established diagnosis and hospitalization in patients with salmonellosis. DALY was 19.9 or 0.96 DALY per 100,000 population. The value of productivity losses was 6,637,665 denars or €107,930. Conclusion: This is the first national study of salmonellosis burden and should serve as an important resource for focusing activities that will reduce this burden. The findings of the study could be the basis for the development of strategies at the regional and national level.

ЈАВНО ЗДРАВЈЕ

ПРОЦЕНКА НА ОПТОВАРУВАЊЕТО СО САЛМОНЕЛОЗА ВО РЕПУБЛИКА СЕВЕРНА МАКЕДОНИЈА

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Извадок

Болестите поврзани со храната сè уште предизвикуваат значаен јавноздравствен, економски и социјален товар ширум светот. Секоја година, 1 од 10 луѓе се разболуваат од храна контаминирана со микроби или хемиски агенси, што резултира со 600 милиони болести, 420 000 смртни случаи и губење на 33 милиони години здрав живот на глобално ниво. Целта на оваа студија беше да се утврди оптовареноста на инфекции предизвикани од на национално ниво и да се утврди јавноздравственото и економско влијание. Материјал и методи: Користени се податоци од националната база на податоци за заразни болести за 2019 година; утврдена е инциденцијата, изгубени години на живот (YLL), години изгубени поради инвалидитет (YLD), години на живот приспособени според инвалидитет (DALY) и економски загуби. Резултати: Анализата опфати 197 пациенти со салмонелоза, од кои 101 или 51,3% беа пациенти од машки пол и 96 или 48,7% пациенти од женски пол. Најголем број случаи имаше во XI месец (ноември) - 46 случаи. Најзастапена возрасна група беа децата на возраст од 0-5 години (79 пациенти). Најголем број случаи беа регистрирани во Скопје - 80 случаи (40,6%). Анализата на податоците покажа значајна поврзаност помеѓу клинички утврдената дијагноза и хоспитализацијата кај пациенти со салмонелоза. DALY изнесува 19,9 или 0,96 DALY на 100 000 жители. Вредноста на загубите во продуктивноста е 6.637.665 денари или 107.930 €. Заклучок: Ова е прва национална студија за оптоварувањето со салмонелоза и треба да послужи како важен ресурс за фокусирање на активностите што ќе го намалат овој товар. Наодите од студијата би можеле да бидат основа за развој на стратегии на регионално и национално ниво.

Introduction

"Disease burden" is defined as the incidence and/or prevalence of morbidity, disability, and mortality associated with acute and chronic disease manifestations.[1] The overall burden of disease is estimated using various composite measures of population health status such as DALY, which is a time-based measure that combines years of life lost due to premature mortality and years lost from life due to the time of living in disability or conditions with impaired health.[2]

Food-borne diseases (FBD) still cause a significant public health, economic and social burden worldwide. Recognizing the need to measure the burden and distribution of FBD and encourage evidence-informed policies, in 2015 the World Health Organization (WHO) published the first estimates of global and regional disease burden for 31 foodborne hazards.[3] The results showed that, each year, 1 in 10 people become ill from food contaminated with microbes or chemical agents, resulting in 600 million illnesses, 420,000 deaths and loss of 33 million healthy life years globally.4 While these estimates were critical to raising awareness, they were the product of a massive research initiative that faced significant data gaps. They significantly did not offer the precision needed to identify priorities at the national level, and were not always able to use all data from available resources. Accurate national estimates of the burden of disease are essential to identify the most important diseases and hazards in a country, as well as the foods that contribute most to these diseases and the interventions needed to effectively prevent them.[5]

The Foodborne Burden of Disease Epidemiology Reference Group (FERG) was established by WHO in 2007 to estimate the global and regional burden of FBD (across the six WHO regions). Other FERG goals were to strengthen the capacity of countries to assess their FBD burden, and to increase the number of countries that have undertaken such a study. FERG activities to promote national studies have included building capacity and promoting the use of disease burden information in evidence-informed policy making. The FERG Study Task Force (CSTF) has developed a suite of tools and resources to support national studies. Pilot studies were conducted in Albania, Japan, Thailand and Uganda and provided important practical lessons. In particular, data gaps hampered DALY calculations on several occasions. These gaps included information needed to assign etiology for syndromes, such as acute gastrointestinal disease, and data on the incidence of diseases caused by some hazards.[6]

It is useful to prioritize FBD burden estimates in food security policies and allocate resources where food security risks are highest. The experiences of established studies and their mechanisms of translating evidence into policy can provide guidance and suggest processes for cooperative national studies.[7]

WHO is supporting countries to estimate the national burden of FBD through technical assistance and the development of guidance for estimating the burden of FBD caused by microbial agents. The guidance includes a complete picture of the requirements, enabling factors, challenges and opportunities for assessing the

burden of FBD and the steps for performing the assessments.[5,8]

The aim of this study was to determine the burden of infections caused by *Salmonella spp*. related to unsafe food at national level, and to determine the public health impact and the economic impact.

Sub-objectives of the paper were:

- To determine the incidence and morbidity of *Salmonella spp*. related to unsafe food during 2019;
- To determine the burden of *Salmonella spp*. through DALY indicator;
- To determine the economic impact of *Salmonella spp*. related to unsafe food.

Material and methods

Data from the National database for infectious diseases from the Institute of Public Health of the Republic of North Macedonia for 2019 was used. Family physicians are obliged to fill out a mandatory notification for infectious diseases at each occurrence of an infectious disease among patients. These records are delivered to the Centers for Public Health and further the information is forwarded to the Institute of Public Health of RNM.

This study includes a DALY measure, which combines information on morbidity, mortality and disability caused by diseases. DALY is a more comprehensive metric than incidence or prevalence rate; it is now the most widely used public health metric for disease burden studies and the key measure in the Global Burden of Disease (GBD) Study.

DALY is a metric of the health gap, a measurement of years of healthy life lost due to a disease or risk factors. DALYs are calculated by adding the number of years of life lost due to premature mortality (YLL) and the number of years lived with disability (YLD), adjusted for severity:

DALY=YLL+YLD

YLL is the product of the number of deaths (M) and the average remaining life expectancy (RLE) at the time of death:

YLL=M x RLE

The 2010 GBD study introduced an approach to calculating burden of disease – a prevalence-based approach. This approach reflects the current burden of disease as a result of past events. In other words, the health status of a population is assessed at a point in time, and prevalent diseases are attributed to initial events that occurred in the past. The definition of YLL is the same as in the incidence-based approach, but YLD is defined as the product of the number of prevalent cases (P) and the disability weight (DW), which reflects the reduction in health-related quality of life on a scale of 0 (no effect on full health) to 1 (death).

YLDprev=P x DW

To estimate YLL, the use of a standard life table is recommended. YLLs reflect the ideal life expectancy, based on the lowest possible mortality given the currently available data. There are different standard life tables developed for the WHO Global Health Assessment (GHA) and GBD studies by the Institute for Health Metrics and Evaluation (IHME), but in this study we used the life table for the Republic of North Macedonia.

The weight of each health outcome is represented by disability weights

(DW). The DW value is between 0 and 1, where 0 represents full health and 1 represents death. DW can be interpreted as a proportional decrease in good health due to an unfavorable health condition. DW for *Salmonella spp*. is 0.101.

Given the difficulty of making detailed estimates of the value of YLL or YLD, a frequently used shortcut is to use a country's per capita gross domestic product (GDP) as a measure of lost productivity. For every year lost to illness, disability or premature death, the country loses the economic output associated with that year. Foodborne disease is therefore represented as a drain on the country's productivity. The calculation is represented by the following formula:

$$VPi = Bi \times Yi$$

where VPi is the value of productivity losses associated with foodborne diseases in country i; Bi is the total DALY burden of foodborne diseases in country i; and Yi is GDP per capita for country i. We expressed this value in local currency (denars) or in euros to make comparison between countries.

Chi-square, Kolmogorov-Smirnov one- or two-sample test, and Fisher exact test were used to compare specific features between two groups. Cramer'V was used to determine the association between two nominal variables.

Results

During 2019, 197 patients with salmonellosis were registered, of which 101 or 51.3% were male patients and 96 or 48.7% were female patients.

The analysis found a non-significant difference between male and female patients (Chi-square:0.127; df=1; p=0.722).

Regarding the month of disease occurrence, the largest number of salmonellosis cases occurred in month XI (November) - 46 cases, followed by month X (October) - 37 cases. The lowest number of cases occurred in month II (February) - 4 cases, and then in month IV (April) - 5 cases. The structure of salmonellosis cases by month is shown in Figure 1, which shows the trend of the increase of the disease during the year.

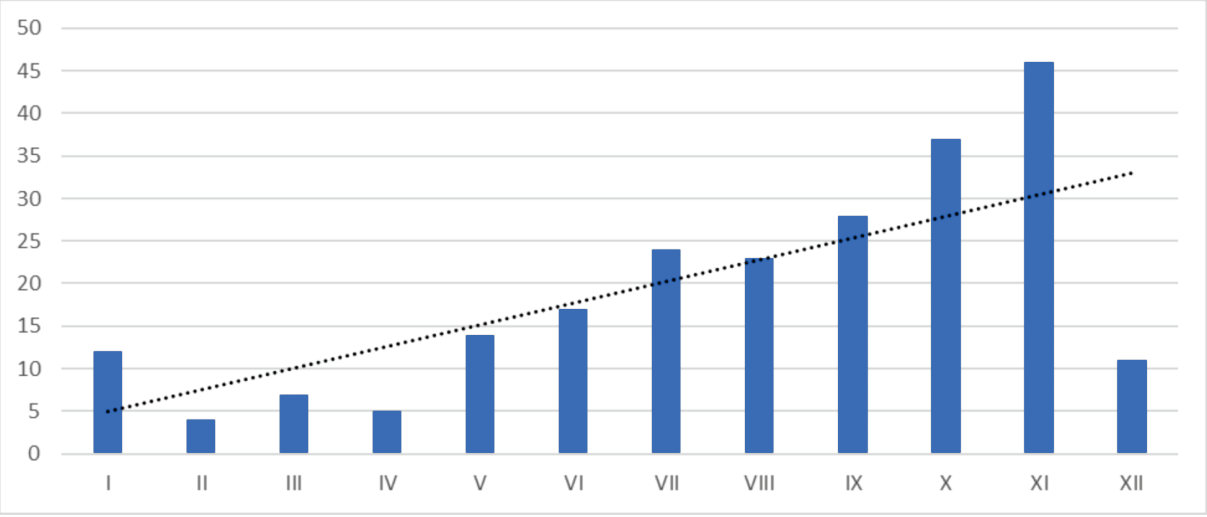

Figure 1. Number of salmonellosis cases by month

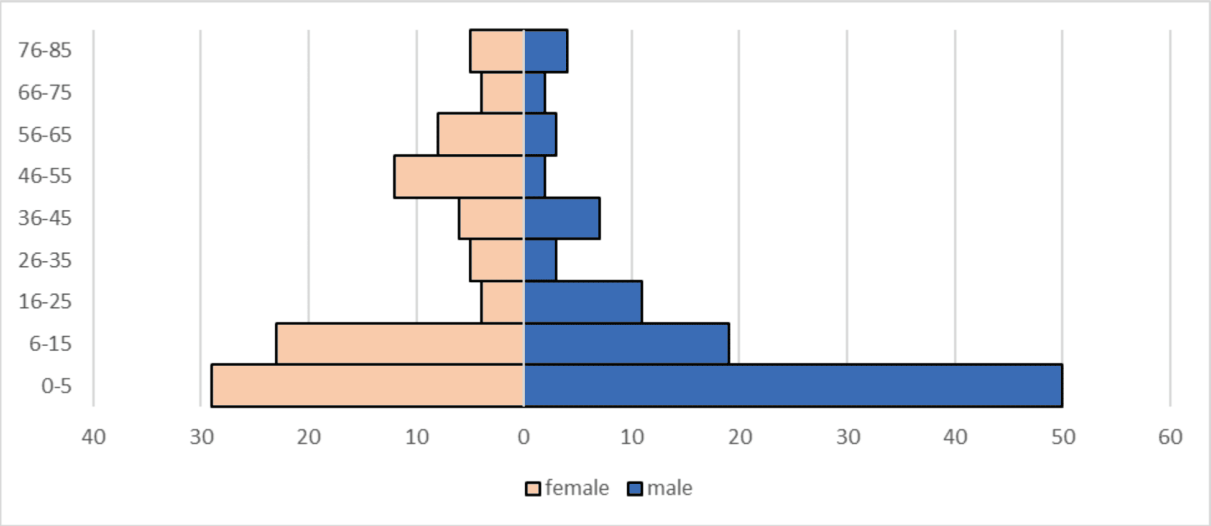

Figure 2. Presentation of the age pyramid for salmonellosis in 2019

Regarding the age of patients, the most represented age group among female patients was 0-5 years (29 patients), followed by the age group 6-15 years (29 patients). The least represented female age group was 16-25 years and 66-75 years with 4 patients. Regarding male patients, the most represented age group was 0-5 years (50 patients), followed by the age group 6-15 years (19 patients). The structure by age groups of patients is shown in Figure 2.

In 2019, the highest number of cases of salmonellosis were registered in Skopje - 80 cases (40.6%), followed by Kumanovo - 22 cases (11.2%). In the same period, the lowest number of cases were registered in Debar, Kavadarci, Negotino and Pehchevo with only one case each (0.5%). The presentation of salmonellosis cases by municipalities is illustrated in Figure 3.

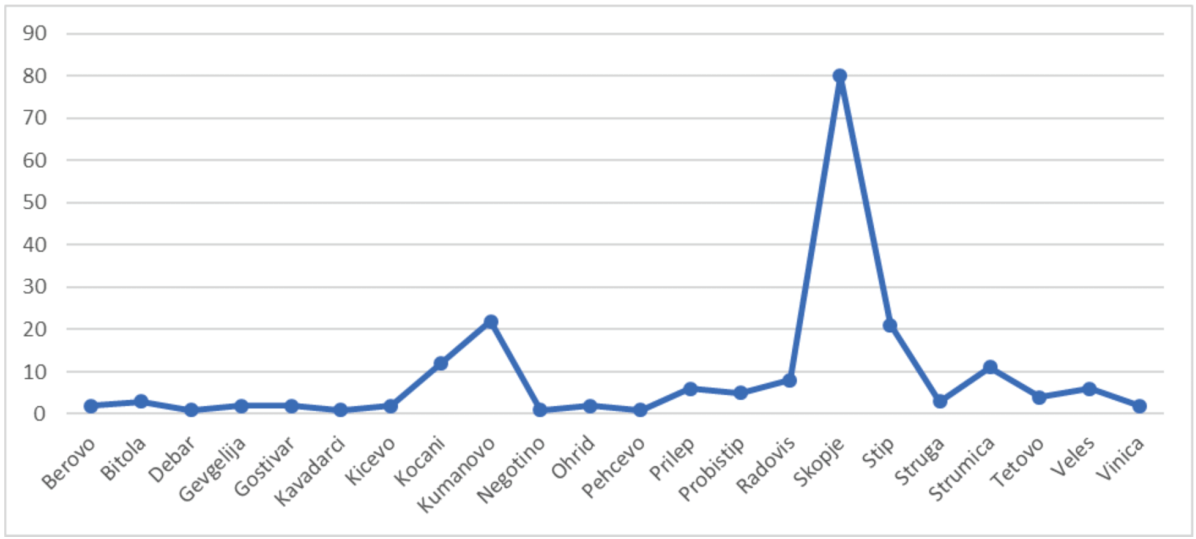

Figure 3. Presentation of Salmonellosis cases by municipalities in 2019

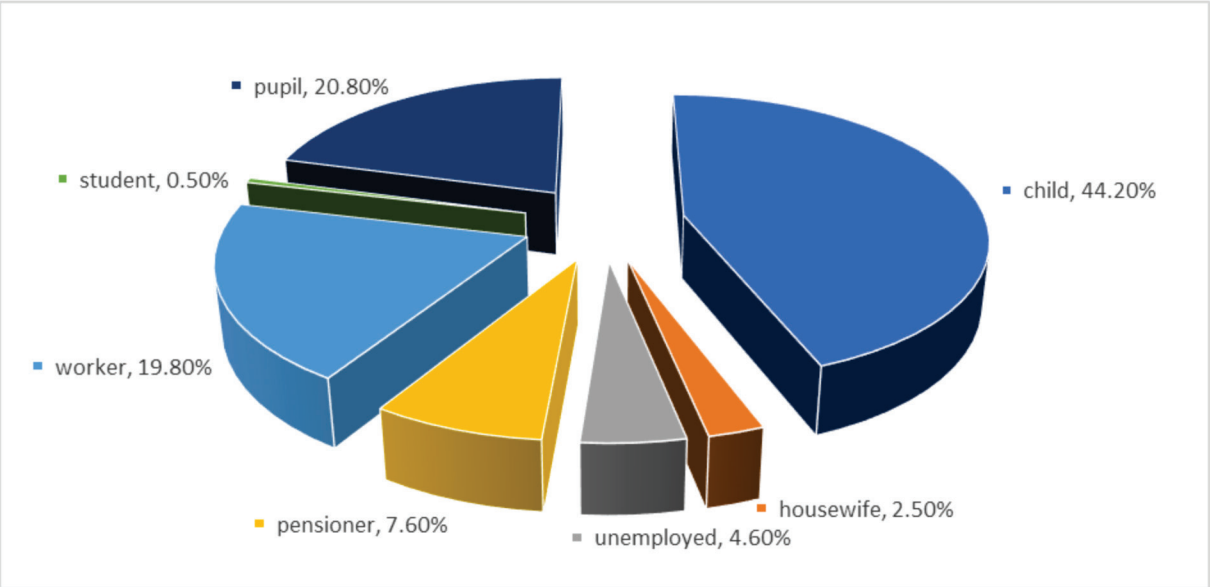

Figure 4. Structure of persons infected with salmonellosis

The analysis of the structure of individuals infected with salmonellosis, in terms of work status, showed that 87 (44.2%) were children, 41 (20.8%) were pupils, one patient was a student (0.5%), 39 (19.8%) were workers, 9 (4.6%) unemployed, 5 (2.5%) housewives and 15 (7.6%) were retired persons. (Figure 4).

The difference between persons with salmonellosis in terms of work status was significant (Kolmogorov-Smirnov Z:3.774; p<0.001)

Table 1. Hospitalization for salmonellosis according to gender

		Hospitalization		Total
		yes	no	
Gender	male	31 (15.7%)	70 (35.5%)	101 (51.3%)
	female	37 (18.8%)	59 (29.9%)	96 (48.7%)
Total		68 (34.5%)	129 (65.5%)	197 (100%)

Regarding hospitalization, the analysis showed that male patients were hospitalized in 31 cases (15.7%), while female patients were hospitalized in 37 cases (18.8%) (Table 1).

The analysis showed a non-significant difference between male and female patients in terms of hospitalization (Chi-square: 1.341; df=1; p=0.247).

Table 2. Hospitalizations for salmonellosis by work status in 2019

		Hospitalization		Total
		yes	no	
Gender	children	33 (16.8%)	54 (27.4%)	87 (44.2%)
	pupils	15 (7.6%)	26 (13.2%)	41 (20.8%)
	students	0	1 (0.5%)	1 (0.5%)
	workers	12 (6.1%)	27 (13.7%)	39 (19.8%)

	unemployed	3 (1.5%)	6 (3.0%)	9 (4.6%)
	housewives	0	5 (2.5%)	5 (2.5%)
	pensioners	5 (2.5%)	10 (5.1%)	15 (17.6%)
Total		68 (34.5%)	129 (65.5%)	197 (100%)

Regarding hospitalization for salmonellosis by work status, the analysis showed that the largest number of hospitalized patients were children - 33 (16.8%), followed by pupils - 15 (7.6%). There were no hospitalized patients with working status, students and housewives (Table 2).

The analysis showed a non-significant difference between patients by work status in terms of hospitalization (Fisher's Exact Test: 3.660; p=0.758).

Data analysis determined a non-significant association between laboratory-confirmed diagnosis and hospitalization among patients with salmonellosis (Cramer's V:0.117; p=0.099).

Data analysis showed a significant association between clinically confirmed diagnosis and hospitalization in patients with salmonellosis. Most patients who were hospitalized had a clinically confirmed diagnosis (Cramer's V:0.223; p=0.002).

DALYs and economic burden of *Salmonella spp.*

The morbidity rate was 9.49 per 100,000 inhabitants.

Mb = (197/2076255) x 100,000 = 9.49 (5).

The sex-specific morbidity rate was 9.26 per 100,000 people for women and 9.71 per 100,000 people for men.

$Mb_{Females}$ = (96 / 1036736) x 100,000 = 9.26

Mb_{Males} = (101 / 1039958) x 100,000 = 9.71

The rate of specific morbidity by work status was 5.08 per 100,000 population for workers and 8.42 per 100,000 population for unemployed (unemployed + housewives).

$Mb_{workers}$ = 39 / 797651 x 100 000 = 5.08

$Mb_{unemployed}$ = 14 / 166363 x 100 000 = 8.42

The incidence rate was 0.095 per 1,000 population.

Incidence rate = (197/2076255) x 1000 = 0.095

DALY = YLL + YLD (1)

YLL = 0

YLD = 197 x dw = 197 x 0.101 = 19.9

dw for Salmonellosis dw = 0.101

DALY = 0 + 19.9 = 19.9

DALY was 19.9 or 0.96 DALY per 100,000 population

DALYfemales = 0 + (96 x 0.101) = 0 + 9.7 = 9.7 (11)

DALYmales = 0 + (101 x 0.101) = 0 + 10.2 = 10.2 (12)

The value of productivity losses was 6,637,665 MKD or 107,930 €

DALY x GDP = 19.9 x 333 551 MKD = 6 637 665 MKD

Discussion

A study on the global burden of disease associated with unsafe food found that *Salmonella spp*. caused 78,707,590 cases of disease worldwide in 2010. Salmonella was responsible for 59,153 deaths in the same year. It caused 4,067,920 DALYs and 78,306 YLDs and 3,976,380 YLLs.[9]

In SEAR B and SEAR C (South East Asian subregion) the burden was 59 DALYs and 58 DALYs per 100,000 population, respectively. In the Eastern Mediterranean region, a burden was found in EMR B with 50 DALYs and in EMR D with 67 DALYs per 100,000 population. In the North American region, the lowest prevalence of diseases related to unsafe food was observed in AMR A with 9 DALYs, AMR B with 11 DALYs and AMR D with 14 DALYs per 100,000 population. In the European region, in EUR A with 12 DALYs, in EUR B (where the Republic of North Macedonia belongs) with 12 DALYs I EUR C with 11 DALYs per 100,000 population. In the Western Pacific region, a burden was found in WPR A and WPR B with 9 DALYs per 100,000 population.[9]

According to the results obtained in our study, *Salmonella spp*. caused a burden of 19.9 DALYs or 0.96 DALYs per 100,000 population which was lower than in the European Region

Numbers were also high in the WHO European Region, where non-typhoidal *Salmonella spp*. took the first place in the ranking of DALYs and deaths due to food hazards, causing 107,000 DALYs and 1854 deaths per year. The median DALY rate was 8 (95% UI 5–14) DALYs per 100,000 population per year. In addition, non-typhoidal Salmonella spp. was estimated to cause 1.7 million cases of illness annually, making it the third most common cause of foodborne illness in the region[10].

In 2014, in the European Union alone, there were over 85,000 reported cases of human salmonellosis, with 65 deaths. The two most commonly reported *Salmonella* serovars in the European Union were *S. Enteritidis* and *S. Typhi*. The European Food Safety Authority (EFSA) estimated that the overall economic burden of human salmonellosis may be as high as 3 billion per year. A significant downward trend in human salmonellosis in the European Union was observed, which was attributed to the joint actions of many actors, including enhanced control programs of *Salmonella spp*. for poultry[11].

In total, 90,105 cases of salmonellosis in humans were reported from 28 EU Member States in 2019. Of these, 87,923 were confirmed cases resulting in an EU reporting rate of 20.0 cases per 100,000 population. This was at the same level as in 2018 (20.1 cases per 100,000 inhabitants). As in the previous year, the highest rates in 2019 were reported by the Czech Republic (122.2 cases per 100,000 population), Slovakia (91.6 cases per 100,000 population), Hungary (45.6), Croatia (32.1), France (27.8), Malta (26.5), Lithuania (26.3), Latvia (2.8) and Belgium (22.1 per 100,000 population), while the lowest rates were reported by Cyprus, Greece, Ireland, Italy, Portugal and Romania (≤ 7.1 cases per 100,000 population).[12]

According to the results of our study, salmonellosis was registered in 197 cases or a rate of 9.49 per 100,000 population, which was lower than the rate in the European Union, but some European countries, such as Bulgaria (8.5 per 100,000 population) and the Netherlands presented similar results (10.8 per 100,000 population).

In total, 15 EU member states provided information on hospitalization. The proportion of confirmed

cases with known hospitalization information was 44.5% at EU level. Among them, the percentage of hospitalized cases was 42.5%, which was approximately at the same level as in 2018. The highest proportions of hospitalized cases were reported, as in previous years, in Cyprus, Greece, Lithuania, Poland and the United Kingdom, where majority of patients were hospitalized. The high percentage of hospitalized cases was probably due to the surveillance focus on severe diseases requiring hospital care. Two of these countries also reported the lowest reporting rates for salmonellosis, indicating that the surveillance systems in these countries primarily recorded the more severe cases.[13]

According to the results of our research, 34.5% of those infected with Salmonellosis were hospitalized.

In total, 17 EU member states provided salmonellosis outcome data and, among them, 11 member states reported 140 fatal cases resulting in an EU fatality rate of 0.22%. Here 46 deaths (32.9%) were reported by the United Kingdom.[12]

In a study conducted in Japan in 2011, it was determined that non-typhoid *Salmonella spp*. 3145 DALYs.[13]

A 2009 study from Thailand found that the incidence of *Salmonella spp*. infections was 1.74.[14]

Salmonella spp. ranks third as a cause of foodborne illness (12%), second as a cause of hospitalization (24%), and first as a cause of death (27%) in France[15]. In the EU, there are more than 91,000 reported Salmonella infections each year[16]. In 2016, 94,530 human salmonellosis cases were reported in the EU, of which *S. enteritidis* accounted for 59% of all cases.

There was also an 11.5% increase in the trend of reported foodborne outbreaks compared to 2015 and *S. enteriditis* was responsible for one in six outbreaks in 2016. Salmonella was responsible for the greatest health burden with 1766 hospitalizations (45,6%) and 50% of all deaths in epidemic cases[17]. In Australia, gastroenteritis was responsible for an estimated $811 million annually in costs associated with treatments, deaths, lost productive hours, and government oversight[18].

From 2009 to 2015 there was a dramatic increase in hospitalizations due to salmonellosis among EU/EEA member states. The joint efforts of the European Commission and stakeholders tried to match the number of cases to 12,510 hospitalizations in 2015. However, recent data shows that the trend is rising again with 16,816 registered hospitalizations in 2018. The USDA ERS[19] estimated the economic cost of Salmonella (non-typhoidal) as $3.66 billion for 2014 considering lost wages, medical costs, premature deaths, caseloads, and lost productivity. In the EU, these costs are estimated to exceed €3 billion per year[20].

In terms of annual costs for Salmonella in Sweden, they amounted to 25.3 million euros, ranking second, just behind Campylobacter[21].

Conclusion

This is the first national study of salmonellosis burden and should serve as an important resource for focusing activities that will reduce this burden. This requires a sustained,

multi-sectoral response from the competent authorities and sectors in the country, including the implementation of food safety standards and effective surveillance networks at national, regional and global level. This will require concerted efforts by all stakeholders in the food chain, from primary production to consumers. The diversity of food hazards indicates the need for a multifaceted strategy, with priorities tailored to each region. While national studies may further refine priorities and are highly recommended, the current findings could already be the basis for developing strategies at regional and national levels.

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