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Economic burden of pneumococcal infections in children under 5 years of age

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ABSTRACT

The present study aimed to determine the cost of childhood pneumococcal infections under 5 years of age and to provide further data for future health economy studies. Electronic medical records of children diagnosed with meningitis caused by *S. pneumoniae* and all-cause pneumonia, and acute otitis media (AOM) between January 2013–April 2014 were retrospectively evaluated. Direct costs for the treatments of hospitalized patients (pneumonia and pneumococcal meningitis) including costs of healthcare services consisted of costs of hospital bed, examination, laboratory analyses, scanning methods, consultation, vascular access procedures, and infusion and intravenous treatments. Direct costs for patients (AOM) treated in outpatient setting included constant price paid for the examination and cost of prescribed antibiotics. Indirect costs included cost of work loss of parents and their transportation expenses. Data of 130 children with pneumococcal meningitis (n = 10), pneumonia (n = 53), and AOM (n = 67) were analyzed. The total median cost was €4,060.38 (direct cost: €3,346.38 and indirect cost: €829.18) for meningitis, €835.91 (direct cost: €480.66 and indirect cost: €330.09) for pneumonia, and €117.32 (direct cost: €17.59 and indirect cost: €99.73) for AOM. The medication cost (p = 0.047), indirect cost (p = 0.032), and total cost (p = 0.011) were significantly higher in pneumonia patients aged ≥36 months than those aged <36 months; however, direct cost of AOM were significantly higher in the patients aged <36 months (p = 0.049). Results of the present study revealed that the treatment cost was significantly enhanced for hospitalization and for advanced disease. Thus, preventive actions, mainly vaccination, should be conducted regularly.

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Introduction

Pneumonia, meningitis, and acute otitis media (AOM) are substantial pediatric public health problems worldwide.¹ In this group of diseases, *Streptococcus pneumoniae* (pneumococcus) is the major global etiological cause of pneumonia and accounts for 36% of overall childhood pneumonia.² As invasive *Haemophilus influenzae* type b infections decrease, pneumococcus has become the leading cause of bacterial meningitis among children aged 5 years or below and is also isolated in 28%–55% of middle ear aspirates from AOM cases.³

According to the World Health Organization (WHO) estimates, approximately 1.6 million people die of pneumococcal diseases each year⁴ and 0.7–1 million of these deaths occur in children under the age of 5 years.² Although case fatality rate due to pneumococcal infections is substantially high in developing countries, it is also considerable in developed countries. While case fatality rate of pneumococcal meningitis was reported as 48% in hospitalized children in Gambia,⁵ this rate has been reported as high as 20% in developed countries.⁶ According to the results of a study evaluating the global disease burden of pneumonia in children under the age of 5 years,

pneumococcal diseases accounted for approximately 11% of overall deaths.¹ Further analyses of the same study revealed that the mortality rate was 119 (87–130) per 100,000 and the case-fatality rate was 5% (4%–9%) for pneumococcal pneumonia; however, for pneumococcal meningitis, the case-fatality rate was as high as 59% (27%–80%) despite the mortality rate of 10 (4–13) per 100,000. Within the European region (including Turkey) identified by WHO, the mortality rate was 25 (18–28) per 100,000 and the case-fatality rate was 5% (4%–9%) for pneumococcal pneumonia, whereas these rates were 3 (2–4) per 100,000 and 38% (32%–58%), respectively, for pneumococcal meningitis. The differences in quality and accessibility of healthcare services may create differences between countries.

According to the global epidemiological data, more than 90% of pneumonia-related deaths in children under the age of 5 years occur in 40 countries, with the highest mortality rates in India, Pakistan, Bangladesh, and Afghanistan.⁷ When inter-continental distribution of pneumonia-related death is evaluated in this age group, sub-Saharan Africa and South Asia show similar distribution.⁸

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Table 1. Direct and indirect costs for the treatments of the study population.

		Pneumococcal Meningitis n = 10	Pneumonia n = 53	Acute Otitis Media n = 67
Direct costs, €	Mean ± SD	9,299.98 ± 13,762.01	1,317.76 ± 3,179.1	20.57 ± 7.64
	Median (Q1-Q3)	3,346.38 (941.82–11,700.86)	480.66 (202.36–891.13)	17.59 (17.59–17.59)
Service cost	Mean ± SD	6,889.99 ± 11,532.51	879.84 ± 2,255.03	NA
	Median (Q1-Q3)	1,794.41 (648.83–8,914.87)	296.69 (175.60–574.53)	NA
Medication cost	Mean ± SD	1,719.31 ± 2,698.07	331.92 ± 1,142.81	NA
	Median (Q1-Q3)	485.24 (275.35–2,068.33)	68.2 (31.33–230.44)	NA
Material cost	Mean ± SD	690.68 ± 1,170.44	106 ± 324.31	NA
	Median (Q1-Q3)	322.84 (24.16–615.96)	8.08 (1.84–50.88)	NA
Indirect costs, €	Mean ± SD	2,472.32 ± 3,078.55	474.23 ± 448.67	106.15 ± 30.45
	Median (Q1-Q3)	829.18 (483.65–3,255.39)	330.09 (214.91–560.44)	99.73 (99.73–99.73)
Total Cost, €	Mean ± SD	11,772.3 ± 16,688.16	1,792.00 ± 3,472.51	126.72 ± 36.07
	Median (Q1-Q3)	4,060.38 (1,463.87–14,959.24)	835.91 (405.31–1,458.12)	117.32 (117.32–117.32)

SD, standard deviation; Q1, 1st quartile (25th percentile); Q3, 3rd quartile (75th percentile); NA, not available

In Turkey, although detailed data about respiratory tract infections are limited, the Turkey Burden of Disease Study conducted between 2002 and 2004 by the Ministry of Health reported that the ratio of disability adjusted life years (DALY) caused by respiratory tract infections were 13.4% in 0–4 year age group and 6.5% in 5–14 year age group.⁹ Additionally, the estimated annual number of cases was 250 for meningitis, 250,000 for pneumonia, and 2.5 million for AOM in Turkey,¹⁰ although data on the contribution of *S. pneumonia* to overall pediatric respiratory tract infections is not fully known due to lack of surveillance data. The present study aimed to determine the cost of childhood pneumococcal infections, which are major public health problems in Turkey as well as globally, under the age of 5 years and to supply a source for further researches on this issue.

Results

The study data was comprised of 10 hospitalized patients diagnosed with pneumococcal meningitis, 53 hospitalized patients diagnosed with pneumonia, 67 patients diagnosed with AOM treated in an outpatient setting, 2 patients who received ventilation tube insertion, and 1 patient who developed hearing loss due to AOM. Of the patients diagnosed with pneumococcal meningitis, 60% were boys and the median (Q1-Q3) age was 28.87 months (7.00–41.93 months), of the patients diagnosed with pneumonia, 52.8% were boys and the median (Q1-Q3)

age was 39.80 months (30.27–45.63 months), and of the patients diagnosed with AOM, 62.7% were boys and the median (Q1-Q3) age was 29.10 months (13.43–43.67 months).

The median (Q1-Q3) values of direct costs and indirect costs were €3,346.38 (€941.82–€11,700.86) and €829.18 (€483.65–€3,255.39), respectively, for pneumococcal meningitis, €480.66 (€202.36–€891.13) and €330.09 (€214.91–€560.44), respectively, for pneumonia, and €17.59 (€17.59–€17.59) and €99.73 (€99.73–€99.73), respectively, for AOM (Table 2). The median (Q1-Q3) values of the total cost were €4,060.38 (€1,463.87–€14,959.24) for pneumococcal meningitis, €835.91 (€405.31–€1,458.12) for pneumonia, and €117.32 (117.32–117.32) for ambulatory treatment of AOM (Table 1).

For two cases who received ventilation tube insertion due to AOM, costs were calculated separately. Accordingly, the median (Q1-Q3) values for direct and indirect costs were €351.33 (€197.24–€505.41) and €441.31 (€406.89–€475.73), respectively and the median (Q1-Q3) value of the total cost was €792.63 (€672.97–€912.30). For one patient who developed hearing loss as a complication of AOM, the direct and indirect costs were €32.41 and €310,411.89, respectively and the total cost was €310,444.30.

The resulting national economic burden is approximately 1 million Euros (direct cost: approximately 0.8 million Euros) for pneumococcal meningitis, approximately 209 million Euros (direct cost: approximately 120 million Euros) for pneumonia, and approximately 293 million Euros (direct cost:

Table 2. Comparison of costs according to age in the patients with pneumonia and acute otitis media.

		Pneumonia			Acute otitis media		
		<36 months n = 21	≥36 months n = 32	p	<36 months n = 40	≥36 months n = 27	p
Direct Costs, €	Mean ± SD	397.65 ± 247.43	1,921.59 ± 3,995.47	0.061	22.08 ± 9.33	18.33 ± 3.00	0.049
	Median (Q1-Q3)	285.38 (202.36–522.01)	601.27 (235.23–1,885.74)		17.59 (17.59–22.93)	17.59 (17.59–17.59)	
Service cost	Mean ± SD	284.35 ± 156.53	1,270.62 ± 2,848.92	0.056	NA	NA	—
	Median (Q1-Q3)	217.77 (175.60–348.18)	438.28 (181.09–999.65)				
Medication cost	Mean ± SD	81.74 ± 78.69	496.1 ± 1,454.83	0.047	NA	NA	—
	Median (Q1-Q3)	53.11 (30.29–97.02)	113.66 (36.67–388.87)				
Material cost	Mean ± SD	31.55 ± 64.53	154.86 ± 409.29	0.490	NA	NA	—
	Median (Q1-Q3)	8.08 (1.43–18.40)	6.83 (2.45–84.68)				
Indirect Costs, €	Mean ± SD	300.83 ± 141.53	588.03 ± 539.45	0.032	109.52 ± 38.78	101.16 ± 7.39	0.215
	Median (Q1-Q3)	291.69 (176.52–368.48)	406.87 (214.91–752.4)		99.73 (99.73–99.73)	99.73 (99.73–99.73)	
Total Cost, €	Mean ± SD	698.48 ± 375.22	2,509.62 ± 4,335.26	0.011	131.32 ± 45.51	119.49 ± 10.26	0.051
	Median (Q1-Q3)	577.08 (378.88–927.09)	1,031.36 (545.02–2,772.51)		117.32 (117.32–122.67)	117.32 (117.32–117.32)	

SD, standard deviation; Q1, 1st quartile (25th percentile); Q3, 3rd quartile (75th percentile); NA, not available

approximately 44 million Euros) for AOM when total costs (and direct costs) per patient are adjusted for the annual estimated average number of patients with pneumococcal meningitis, pneumonia, and AOM (250; 250,000; and 2,500,000, respectively, in Turkey before implementation of 13-valent pneumococcal conjugate vaccine [PCV]). The total economic burden of pneumococcal infections in, excluding bacteremia, is therefore approximately 500 million Euros (total direct cost: approximately 165 million Euros).

Comparison between age groups revealed that medication cost ($p = 0.047$), indirect cost ($p = 0.032$), and total cost ($p = 0.011$) were significantly higher in pneumonia patients aged ≥ 36 months than those aged < 36 months (Table 2). Direct cost of AOM was significantly higher in the patients aged < 36 months than those aged ≥ 36 months ($p = 0.049$). On the other hand, comparison of costs between genders revealed no difference between the groups (Table 3).

Discussion

Childhood respiratory tract infections are associated with high morbidity and mortality. According to the 2014 Health Statistics released by the Turkish Ministry of Health,¹¹ among major health problems occurring during the last 6 months of 2014, the rate of upper and lower (pneumonia, etc.) respiratory tract infections in the 0–6 year age group was 41.9% and 10.1%, respectively. However, there is no national data with regard to the economic burden associated with these diseases, which are seen in more than half of children in this age group.

According to the 2004 National Burden of Disease and Cost Effectiveness Project,¹² pneumococcal meningitis ranks fifth among the first 20 diseases causing death by 2.7% in 0–14 year age group in Turkey. The same report also stated that pneumonia is the second leading cause of mortality by 14% among lower respiratory tract infections. In addition to direct and indirect costs arising from the treatments of these diseases, years of life lost due to mortality also lead to a substantial burden on health-related economic outcomes. Although treatment of these diseases prevents an important portion of resulting mortality, the ratio of DALY caused by these diseases to overall DALY is 12.6 for 0–14 year age group.¹² In the light of these data, it is obvious that pneumococcal diseases lead to a

substantial burden on health and economic systems of Turkey in terms of economic cost and morbidity as well as mortality-related costs. In the present study, among pneumococcal infections, the highest total cost was estimated for the treatment of pneumococcal meningitis by €4,060.38 per patient followed by pneumonia by €835.91 per patient and AOM by €117.32 per patient. There is a gap of economic burden studies in this area. In a study which evaluated the economic burden of childhood pneumococcal diseases in the Gambia, the median (interquartile range) total societal cost of inpatient pneumonia was US\$87.0 (US\$63.0– US\$129.7) per patient.¹³ In Korea, a nationally representative cross-sectional study evaluated the economic burden of otitis media in 2012 reported the total cost of otitis media in 0–9 year age group as 257.87 million Dollars in the outpatient setting.¹⁴ Since there are differences in health policies as well as in national economies of the countries, these results are not comparable.

In Turkey, national implementation of the 7-valent PCV infant vaccination program followed by the implementation of 13-valent PCV in 2011 is associated with substantial improvements in the prevention of pneumococcal infections. The introduction of PCVs has been associated with a significant reduction both in invasive pneumococcal disease (IPD) and mucosal pneumococcal diseases in many countries. Following the introduction of PCV13 in the USA, IPD incidence decreased by 91% in children below 2 years of age due to the additional 6 serotypes.¹⁵ In the UK, IPD due to PCV13-only serotypes decreased by 89% after the PCV13 National Immunization Program in children below 2 years of age as compared with the pre-PCV13 periods.¹⁶ In Southern Israel, sequential implementation of PCV7 and PCV13 was associated with decreases in otitis media caused by PCV7 serotypes plus serotype 6A and then by 5 additional PCV13 serotypes (5VT: 1, 3, 5, 7F, 19A) by 96% and 85% in the respective periods.¹⁷

The present study has also some limitations. Firstly, being a single center study is one of the limitations. Secondly, the pneumonia cases included in this study were not proven to be caused by *S. pneumoniae*; thus, lobar pneumonia cases were aimed to be included as they best represent pneumococcal pneumonia. Thirdly, only hospitalized patients with pneumonia were included. However, if non-hospitalized pneumonia patients were also included, contributory outcomes could be

Table 3. Comparison of costs according to gender in the patients with pneumonia and acute otitis media.

		Pneumonia			Acute Otitis Media*		
		Girl n = 25	Boy n = 28	p	Girl n = 25	Boy n = 42	p
Direct Costs, €	Mean \pm SD	666.97 \pm 856.55	1,898.83 \pm 4,250.92	0.165	20.39 \pm 7.1	20.67 \pm 8.03	0.696
	Median (Q1-Q3)	272.15 (190.40–649.63)	534.59 (299.37–1,023.96)		17.59 (17.59–17.59)	17.59 (17.59–17.59)	
Service cost	Mean \pm SD	428.36 \pm 478.09	1,282.95 \pm 3038.63	0.247	NA	NA	—
	Median (Q1-Q3)	217.77 (152.72–447.31)	318.81 (200.06–743.65)				
Medication cost	Mean \pm SD	151.83 \pm 238.16	492.71 \pm 1551.79	0.101	NA	NA	—
	Median (Q1-Q3)	55.38 (29.73–123.62)	86.7 (36.67–257.26)				
Material cost	Mean \pm SD	86.78 \pm 310.15	123.17 \pm 341.18	0.345	NA	NA	—
	Median (Q1-Q3)	5.95 (1.18–20.25)	8.91 (1.89–84.68)				
Indirect Costs, €	Mean \pm SD	389.98 \pm 308.75	549.47 \pm 539	0.136	104.34 \pm 12.73	107.23 \pm 37.34	0.781
	Median (Q1-Q3)	291.69 (176.52–560.44)	368.48 (253.3–598.83)		99.73 (99.73–99.73)	99.73 (99.73–99.73)	
Total Cost, €	Mean \pm SD	1,056.94 \pm 1,068.04	2,448.30 \pm 4,611.13	0.130	116.61 \pm 19.00	127.90 \pm 43.26	0.722
	Median (Q1-Q3)	743.29 (361.02–1,210.07)	901.59 (590.03–1,799.23)		109.33 (109.33–109.33)	117.32 (117.32–117.32)	

SD, standard deviation; Q1, 1st quartile (25th percentile); Q3, 3rd quartile (75th percentile); NA, not available

provided both in clinical and economic impact of vaccination. Despite these limitations, this study provides useful insights into economic burden of pneumococcal infections in children (0–5 years old) considering that there is very limited data in this area especially in Turkey. Therefore, further cost studies are needed, particularly in children, to set forth the economic burden of pneumococcal infections.

Conclusions

The present study brings new information and perspectives to the limited local data on the economic burden of childhood pneumococcal infections in Turkey. This study revealed that the treatment cost was significantly higher in hospitalized patients. The cumulative burden of pneumococcal disease on the health care systems elucidates the necessity of effective prevention strategies.

Materials and methods

Electronic data of children under 5 years of age who were treated for meningitis due to *S. pneumoniae*, pneumonia, and AOM in Hacettepe University Hospital from January 2013 through April 2014 were retrospectively evaluated. Children who were diagnosed with pneumonia after 48 hours of hospitalization and were hospitalized 2 days or more within the last 90 days were excluded. The study was approved by the Non-Interventional Clinical Research Ethics Board of Hacettepe University (Approval number: GO 14/290–22).

Direct costs for hospitalized patients with meningitis due to *S. pneumoniae* and with pneumonia included the costs of healthcare services, medications, and materials. Costs of healthcare services consisted of costs of hospital bed, examination, laboratory analyses, scanning methods, consultation, vascular access procedures, and infusion and intravenous treatments. Data regarding costs of healthcare services were obtained from Hacettepe University Hospital, which uses the unit prices indicated in the National Health Practices Statement (HPS) Appendix-2B (UPDATED Statement of Changes 2013 HPS, dated August 30, 2014).¹⁸ Medication costs were determined based on the prices stated on the hospital invoice. Costs of materials consisted of consumables which were used over the course of hospital stay. Since the etiology of pneumonia cannot be accurately estimated as it is technically difficult,¹⁹ the costs for pneumococcal pneumonia were calculated using overall pneumonia cases. Among the overall pneumonia cases, lobar pneumonia cases were selected for cost calculation as they best represented pneumococcal pneumonia. Since the etiology of AOM cases were not known as well, direct costs for overall AOM treated in outpatient setting were calculated according to package pricing -the price paid to Pediatric Infection and Ear Nose Throat outpatient clinics by the Social Security Institution- which included costs of laboratory analyses, drugs used during examination, and the examination fee. The costs for patients requiring ventilation tube insertion due to AOM were calculated separately. Likewise, the costs for patients who developed hearing loss as a complication of AOM were also calculated separately.

Indirect costs for each disease were calculated using the same method. The average monthly gross earnings (€774.14) obtained from the Labor Cost Survey 2012 conducted by Turkish Statistical Institute (TurkStat) were used as the basis of the calculation.²⁰ According to the data from TurkStat, labor force participation rate in February 2014 was 70.0% among males and 28.7% among females.²¹ The rate of employment was adjusted to 90% in fathers and 41% in mothers.²² Daily earnings were determined to be €23.23 ($€774.14 \times 0.90/30$ days) for fathers and €10.58 [$(€774.14 \times 0.41)/30$ days] for mothers. According to the assumptions based on an expert opinion, mothers were assumed to be the primary caretakers and were therefore considered to accrue work loss over the course of a child's hospital stay. The fathers were assumed to have one day of work loss per week over the course of a child's hospital stay. The parents were also supposed to come for the control visits together and thus, it was assumed one day of work loss at each control visit. Workforce losses of the mothers and fathers were calculated by multiplying aforementioned earnings by the number of days of work loss. Expenses for round trip to hospital were calculated by multiplying the number round trips to hospital by €4.59.²³ It was assumed that the fathers had a round trip to hospital every day over the course of his child's hospital stay and that 5 more round trips to hospital arose from mothers making 1 trip to the hospital on the first day of hospitalization and 1 trip from the hospital on the day of discharge and from both mothers and fathers making 4 round trips to the hospital for two control visits after discharge. All costs were expressed in Euros according to the 2014 currency of Turkish Liras (€1.00 = 2.9 Turkish Liras, without inflation adjustment). The probabilistic sensitivity analysis was performed to assess the robustness of the indirect cost estimates, including costs for total round trips and workforce losses of the mothers and fathers, for each disease and the sensitivity analysis range value was $\pm 25\%$ of the base value.

Statistical analysis

Data were analyzed using the Predictive Analytics Software (PASW) version 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as number and percentage for categorical variables and as mean, standard deviation, median (interquartile range) for numerical variables. In comparing two independent groups, Mann-Whitney U test was used for non-normally distributed numerical variables. A p value < 0.05 was considered statistically significant. The human capital approach was used in the productivity loss calculation.

Disclosure of potential conflicts of interest

Mehmet Ceyhan, MD, Prof., received non-financial support from Pfizer, Turkey. Yasemin Ozsurekci, MD, received non-financial support from Pfizer, Turkey. Kubra Aykac, MD, received non-financial support from Pfizer, Turkey. Basak Hacibedel, MSc, is employee of Pfizer, Turkey. Ege-men Ozbilgili, MD, is employee of Pfizer, Turkey.

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