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A literature-based economic evaluation of healthcare preventable adverse events in Europe

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Abstract

Purpose: To establish from the literature, cost of preventable adverse events (PAEs) to member states of the Joint Action European Union Network for Patient Safety and Quality of Care.
Data sources: We searched MEDLINE, EMBASE and CINAHL for studies in Europe estimating cost of adverse events (AEs) and PAEs (2000–March 2016). Using data from the literature, we estimated PAE costs based on national 2013 total health expenditure (THE) data reported by World Health Organization and converted to 2015 Euros.
Study selection/Data extraction: Information on type, frequency and incremental cost per episode or estimated cost of AEs was extracted. Total annual disability-adjusted life years (DALYs) resulting from PAEs in 30 EU nations were calculated using an estimate from a published study and adjusted for the percentage of AEs considered preventable.
Result of data synthesis: Published estimates of costs of AEs and PAEs vary based on the care setting, methodology, population and year conducted. Only one study was from primary care, the majority were conducted in acute care. Nine studies estimated percentage of THE caused by AEs, 13 studies calculated attributable length of stay. We estimated the annual cost of PAEs to the 30 nations in 2015 to be in the range of 17–38 billion Euros, total DALYs lost from AEs as 3.5 million, of which 1.5 million DALYs were likely due to PAEs.
Conclusion: The economic burden of AEs and PAEs is substantial. However, whether patient safety interventions will be 'cost saving' depends on the effectiveness and costs of the interventions.

Key words: adverse event, economic evaluation, patient safety, disability-adjusted life years

Introduction

Adverse events (AEs) are unintended injuries or complications, leading to prolonged hospital stay, disability at the time of discharge or death, and are due to healthcare management rather than to the patient's underlying disease [1, 2]. Some AEs result from errors of commission or omission during treatment and hence may be preventable, but other AEs occur even with the best of care. AEs are significant challenges to all healthcare systems, have considerable economic and social impact, and are linked with the direct medical costs in hospitals and primary care [2, 3]. It is estimated that 8–12% of patients admitted to European hospitals suffer from AEs [4].

Estimates of the burden of AEs among hospitalized patients worldwide suggest that ~43 million AEs occur each year, resulting in the loss of 23 million disability-adjusted life years (DALYs) [5]. Only seven types of in-hospital AEs were investigated by Jha *et al.* [5], although a small proportion of the total, this study confirms that preventable adverse events (PAEs) are a leading cause of morbidity and mortality worldwide [6]. The average excess length of stay (LOS) in Europe due to AEs ranges from 6 to 8.5 days [2, 3]. Reasons for the excess length of hospital stay include new diagnostic tests and new treatments to correct the effect of AEs. That the cost of adverse drug events (ADEs) is substantial, and that ADEs are a major cause of hospitalization, has been proven [2, 7–9]. However, there is a dearth of studies on the cost of healthcare PAEs in Europe.

It is also consistently reported that ~9–11% of hospital admissions are complicated by AEs, of which 43–46% may be preventable [2, 10]. In primary care, AEs affect an estimated average of 7% of patients in a single year, 70% of which may be preventable [10].

Purpose

This study offers a literature-based evaluation of the potential cost of AEs to member states of the Joint Action European Union Network for Patient Safety and Quality of Care (PaSQ) and estimates the additional costs of PAEs to their healthcare systems. It is a sub-project of PaSQ, and one of the many initiatives worldwide to improve patient safety.

Methods

Literature review

Searches

The MEDLINE, EMBASE and CINAHL databases were searched for all articles published between January 2000 and March 2016 using the following search terms as keywords: 'economics', 'cost effectiveness', 'cost', 'cost analysis', 'economic burden', 'adverse event', 'preventable' and 'patient safety'. Google and Google Scholar were also searched for non-peer reviewed reports. Reference lists of all identified studies were searched for relevant papers.

Study selection

Only studies conducted in EU countries, having a concept of AEs based on the World Health Organization (WHO) framework [11], and reporting the types of direct or indirect costs applied were included in this review. All European studies on costs of AEs that fulfilled these criteria were included, irrespective of the type of AEs described (preventable or non-preventable), given the paucity of European studies.

Data extraction

Abstracts of all retrieved articles were screened by one reviewer (T.B.A.) and articles that did not meet inclusion criteria were excluded. Two reviewers (T.B.A. and J.J.M.) independently assessed and extracted data from the selected articles. All relevant articles were reviewed, including articles in English, Spanish and French. An article was included if it met all of the following criteria: specified period, a description of the healthcare system or setting assessed, description of AE types included and a description of the method applied to estimate costs. A template was designed for extracting the following information: country, setting, incidence/prevalence of AEs and PAEs, attributable LOS, cost per episode or estimated cost of AE (including the cost of PAEs where available), estimated percentage of total health expenditure (THE) spent on AEs and where possible, the benefits of patient safety interventions.

Economic analysis

Estimates were made by M.L. regarding two economic effects of PAEs: the direct healthcare costs that result from PAEs and indirect effects linked to the loss of health [12] measured in DALYs. The economic analysis was conducted for 30 European nations—the EU member nations of PaSQ plus Switzerland (see list in Table 2). It was based on the information provided by three studies conducted in Europe, the only studies retrieved by the literature search that provided sufficient cost data for us to estimate PAE costs as percentage of national THE [3, 13, 14]. We also used two other studies conducted outside Europe that made similar estimates [5, 12]; and national statistics published by the WHO [15], United Nations (UNs) [16], International Monetary Fund (IMF) [17] and the European Central Bank (ECB) [18].

Direct healthcare costs

To estimate the direct healthcare costs attributable to PAEs in the 30 nations, the national 2013 THE figures as reported by the WHO [15], given as a percentage of national GDP values, were multiplied by the GDP values provided for the nations by the IMF in US dollars [17]. These US$ estimates for THE were then converted into Euros using the currency exchange rate for 2015 [18] .The upper and lower limits for a range of PAE costs were then estimated by using percentage values reported in the literature [3, 12, 13].

A median PAE/AE ratio of 0.435 (interquartile range: 0.394–0.496) [10] was used to calculate the costs of PAEs in both parts of the economic analysis. This ratio is from a systematic review of six studies [10], all of which used strict definitions and procedures very similar to the Harvard Medical Practice Study [1]. Although data from these studies are not directly comparable, there is reasonable assurance that it was collected according to the standardized protocols.

Cost data provided by two studies [3, 13] enabled us to calculate a range for the national costs of PAEs. Hoonhout *et al.* [3] found that direct healthcare costs of PAEs in hospitals amounted to 1.1% of the annual national hospital budget and used this estimate to extrapolate the cost of PAEs in the THE of the Netherlands. We have used this 1.1% estimate as the lower margin of the range in our analysis. Antoñanzas [13] estimated that AE costs accounted for 5.6% of the cost of the public healthcare system in Spain; we extrapolated this value to the THE. Then, by using a PAE/AE ratio of 0.435 [10], we estimated that PAE costs accounted for 2.43% of the THE and used this figure as the upper margin of the range.

Disability-adjusted life years

To estimate the number of preventable DALYs per year, we assumed that the same rate of DALYs arising from in-hospital AEs would apply in Europe as for all the high-income countries. We calculated the number of DALYs per year by extrapolating the 7.2 million DALYs reported by Jha *et al.* [5] to the population total of the 30 nations (PaSQ nations + Switzerland), based on UNs population statistics [16].

Using the same annual rates as Jha *et al.* [5] for hospitalization (10.8% of population), AEs per hospitalization (14.2%) and DALYs per AE (44.4%), we calculated DALYs per year for the total population of the 30 nations (Table 3). The total number of

preventable DALYs per year (i.e. those resulting from PAEs) was then calculated by applying the PAE/AE ratio of 0.435 [10].

Results

Results of literature review

Initial literature search yielded 1810 citations. We screened out 1769 abstracts that were editorials, studies not conducted in Europe or articles lacking costing information. Figure 1 shows the results of the search and screening process. Full texts of 61 publications were obtained and reviewed. We excluded 41 publications from the review for the following reasons: primary data or analysis was for intervention or treatment ($n = 27$), or no primary data on cost analysis ($n = 14$). In total, 20 papers were considered to meet the inclusion criteria and reviewed for this paper. These studies used a similar definition of AE as 'unintended injury that result in temporary or permanent disability caused by healthcare management rather than the patients' disease'. The degree of preventability of AEs was determined after the review of clinical information by two or more physicians. Nine studies [2, 3, 13, 14, 19–22, 26] extrapolated some data to estimate the percentage of the THE caused by AEs. Only two studies [2, 3] showed the yearly cost of PAEs (see Table 1).

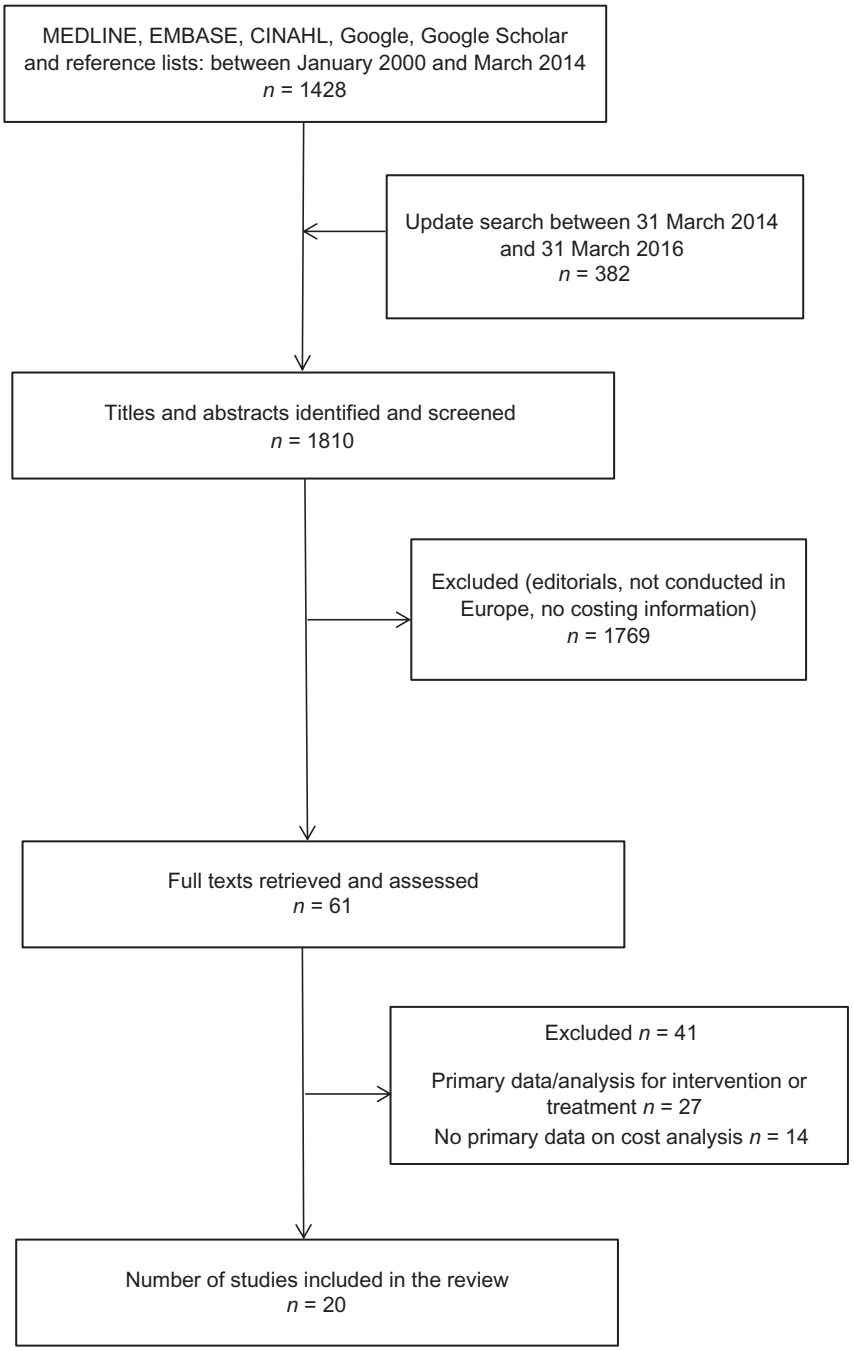

Figure 1 Flow chart of study selection.

Table 1 Summary of EU studies estimating cost and frequency of AEs

Author	Year of publication	Setting and location	Purpose/costs included	Type of AEs included	Frequency of AEs	Attributable LOS	Estimated attributable cost (year)	Total health expenditure
Vincent *et al.* [2]	2001	Two acute hospitals London UK	To make preliminary estimates of incidence and costs of AE/ Additional or excess cost of AEs extracted from patients records. Cost related to LOS	AEs and PAEs	10.8%; 48% judged as PAEs	8.5 days; 46% of LOS judged as preventable	Additional cost: £290 268 €476 620 (2000)	Extrapolated to all hospitals in England and Wales: about £1 billion in extra bed days alone
Plowman *et al.* [21]	2001	NHS hospital, part of a Trust UK	Comprehensive assessment of infection incidence and impact on resource use/Total costs of hospital-acquired infections	HAI	Incidence of HAIs: 7.8%	14.1 days	Mean additional costs due to HAI: £3154 €3738 (1995)	£930.62 million/ €1102.78 million (1995) per year
Nurmi and Luthje [23]	2002	Two nursing homes and two health centre hospitals Finland	Treating fall injuries outside the person's own ward, including costs of transportation for medical treatment	Fall	Incidence of fractures per 1000 person years = 54 in women and 10 in men	Not available	Average of €944 per fall	Not reported
Orsi *et al.* [24]	2002	Hospital, 2000 beds Italy	Cost related to LOS (average daily cost as €400 in the surgical ward and €1200 in the ICU)	Hospital-acquired BSI	2% of patients' experienced BSI. The number of cases and relative incidence varied significantly between wards from 0.2 to 9.6%	Increased LOS attributable to 23.8 days	The cost of increased LOS per patient attributable to BSI was €15 413. The additional cost per patient due to treatment was €943, making the overall direct cost €16 356 per case	Not reported
Pirson *et al.* [22]	2005	Hospital, 278 beds Belgium	To determine extra costs associated with hospital-acquired bacteraemias/cost and LOS for bacteremia	HAB	6.6 per 10 000 days	21.1 days	Average incremental cost of €12 853 and for ICU €11 443 (2001)	€92 960 072 excluding indirect costs
Pirson *et al.* [25]	2008	Three hospitals in 2003 and 2004 Belgium	To determine excess expenditures on HAB	HAB	Incidence rate per admission of 0.39, 0.52 and 1.63%	30 days and 6.1 days in ICU	€19 301 per patient extra cost associated with HAB	Not reported
Defez *et al.* [26]	2008	Hospital, 725 beds France	To estimate the direct additional medical costs of nosocomial Infections/Laboratory test, radiology, surgery, antimicrobial agents rate per day of hospital bed	Nosocomial infections	Not available	Not available	Attributable cost (mean €) by site of infection, UTI: €574 Surgical site: €1814 Respiratory tract: €2421 Bloodstream: €953 Other: €1259	Total additional costs of nosocomial infections (direct medical costs and costs of LOS) estimated as up to €3.2 million per year

Karnon *et al.* [27]	(2008)	400-bed hospital UK	To examine the clinical and economic impact of three approaches to reducing medication errors in hospitals	Medication errors	162 000 prescription/year, incidence of AEs = 432 with no intervention, 263 with CPOE, 286 with ward pharmacists and 362 with bar coding	Not available	Cost–benefit analysis. Net benefits of £31.5, £27.25 and £13.1 million over 5 years for CPOE, ward pharmacists and bar coding, respectively	Not reported
Weber *et al.* [28]	2008	Hospital, 28 000 surgical procedures performed per year Switzerland	LOS, estimation of per diem cost/including rooming, medications and laboratory procedures (€1141). Costs expressed as 2005 €	SSI and PP after head and neck cancer surgery	SSI: 31% PP: 8% SSI and PP: 5%	16.8 additional days	€19 638 per year of LOS	Not reported
Penel *et al.* [29]	2008	Cohort of surgery patients with biopsy proven squamous cell carcinoma of the upper aero-digestive tract France	LOS, estimation of per diem cost, including rooming, medications and laboratory procedures (€1141). Costs expressed as 2005 €	SSI and PP after head and neck cancer surgery	SSI: 31% PP: 8% SSI and PP: 5%	SSI: 16 days in additional mean LOS PP: 17 days SSI and PP: 31 days	SSI: €17 434 increase in mean direct medical costs PP: €19 476 Both SSI and PP: €35 382	Not reported
Hoonhout *et al.* [3]	2009	Twenty-one hospitals Netherlands	To assess total direct medical costs associated with AEs and PAEs/Direct medical costs, based on additional LOS and additional medical procedure	All AEs and PAEs	5.7%; 40% judged preventable	University hospitals: 10.1 days General hospitals: 8.9 days PAEs was 4.4 days	€4446 per AE; €2979 to €6649/PAEs (2004)	€355 million in 2004 (€161 million for PAEs; 15% of total intervention cost attributed to AEs). 2.4% for AEs and 1.1% for PAEs
van Rijen and Kluytmans [30]	2009	Hospital 2001 to 2006 Netherlands	To determine costs and benefits of MRSA Search and Destroy policy *Variable costs*: costs for isolation, contact tracing, treatment of carriers and closure of wards *Fixed costs*: costs of building isolation rooms, salary of a full-time infection control practitioner	MRSA prevented	Not available	Not available	Costs of MRSA policy estimated as €215 559/year, equals €5.54 per admission. Annual saving associated with prevented MRSA bacteraemia was €427 356. The programme saved the hospital €211 797 and 10 lives.	Not reported

Table continued

Table 1 Continued

Author	Year of publication	Setting and location	Purpose/costs included	Type of AEs included	Frequency of AEs	Attributable LOS	Estimated attributable cost (year)	Total health expenditure
Vrijens *et al.* [31]	2010	Nineteen hospitals Belgium	To estimate the effect of HA-BSI on LOS and costs during hospitalization of 1839 patients/Medical acts, medical supplies, pharmaceutical products and cost of stay of €285	Hospital-acquired BSI	Not provided	Increased LOS attributable to BSI was a mean of 9.9 days	Additional cost per infection was €4893	Not reported
Stark *et al.* [32]	2011	Hospitals Germany	To estimate the frequency and cost of ADEs/Hospitalization, Emergency visits, additional treatments, stays in long-term care and death	ADEs	2.14 million adults in 2007		€816 million 58% of costs resulted from hospitalizations, 11% from emergency department visits and 21% from long-term care costs per case in 2007: €381	Not reported
Nestrigue and Or [33]	2012	Hospitals France	Standard hospital day in 2007	Nine specific AEs using patient safety indicators of AHRQ	Not available	0.5% of the hospital stays	Mean incremental cost €500–€15 000 for obstetrics traumas to post-operative sepsis, respectively	Not reported
Antoñanzas [13]	2013	National Health System Spain	To make preliminary estimates costs of AE in primary care and hospitals/cost-to-charge of LOS and care to recovery an AE in primary care. (Standard hospital day €3800, emergency intervention per case €200, physician consultation in primary care €25)	AEs in hospitals and primary care	Not available	6.1 days	€2474 million for hospital (2011) €969 million for primary care (2005)	5.6% of THE
Allue *et al.* [14]	2014	Twelve hospitals Spain	To evaluate the incidence and costs of AEs/Full costing Direct cost of hospitalization	All AEs	6.8%	Not available	16.2% of direct cost. Mean incremental cost: €5260-€11 905/AE (2008–2010)	Extrapolated to €1062 million (3.0% of Spanish hospitals expenditure or 1.5% of THE)
Gyllensten *et al.* [20]	2013	Primary care, other outpatient care and	To estimate COI for individuals with self-reported ADEs and compare estimates with COI for individuals without ADE/	Self-reported ADEs or sub therapeutic effects of medication therapy	19.4%	Not available	Int$442.7 to 599.8 **€318–431** Direct costs: Int$279.6 to 420.0 (67.1%); **€201–302**	Extrapolated to the Swedish population, annual direct

		inpatient care Sweden	*Direct costs* (prescription drugs, healthcare, social services and transportation); *Indirect costs* (costs from sick leave)				Indirect costs: Int$143.0 to 199.8 (32.9%). €103–143 (2011)	costs resulting from ADRs or STEs was Int$ 370.1 million
Palomar *et al.* [34]	2013	All adult ICUs, 17 Health Regions Spain	To assess Bacteremia zero effectiveness after contextual adaptation at large-scale implementation in ICUs	CRBSI	3.07 per 1000 catheter days	12 days	€3103/ICU day Total saving €27 629 112 considering a project cost of €2 340 000742 CRBSI and 66 deaths avoided per year	Not reported
Gyllensten *et al.* [19]	2014	Adult general population Sweden	To estimate the direct costs of ADEs/Drug-related hospitalization, loss of productivity or disability pension	ADEs	12%	Not available	Total cost for patients: $6235.0 (€4259) Direct cost $2831 (€1933) Indirect cost $3405 (€2326) (2008)	USD 21 million per 100 000 adult/ year (i.e. 9.5% of total direct cost)

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; BSI, bloodstream infection; COI, cost of illness; CPOE, computerized physician order entry; HCAIs, healthcare-associated infections; HAIs, hospital-acquired infections; ICU, intensive care unit; PP, post-operative pneumonia; SSI, surgical site infection.

The majority of studies were identified from acute care [2, 3, 21–34]. One study estimated AEs from primary care [13], another two included both inpatients and outpatients in the analysis to estimate the cost of ADEs [19, 20]. The most frequently analysed AEs related to infection [21, 22, 24, 26, 28–31, 34], medication [19, 20, 27, 32] and falls [23]. The types of AEs included and the method for calculating the cost of AEs varied between studies. Most studies analysed direct cost of AEs such as the costs related to LOS or additional medical procedures to repair the effects of AEs. Only the studies conducted in Sweden included indirect cost of AEs such as lost productivity due to sick leave or career leave [19, 20]. Costs were extrapolated in a majority of the studies from estimated cost of treatments or number of days of hospitalization. A full costing approach was applied in a few studies [14, 28, 30, 34], while others used a mixed approach, i.e. extrapolation and full costing for estimates [19, 20, 22, 26].

Attributable LOS was assessed in 13 studies [2, 3, 13, 21, 22, 24, 25, 28, 29, 31–34] and ranged from 6 to 30 additional days; additional LOS was higher for hospital-acquired infections than for other types of AEs. Three studies evaluated the cost–benefit of patient safety interventions. These cost–benefit studies mainly related to a small range of easily definable harm from medication errors [27], methicillin resistant staphylococcus aureus (MRSA) [30] and catheter-related bloodstream infections (CRBSIs) [34], but not to broader safety areas such as diagnostic and treatment delays.

Results of economic analysis

An estimated range of the direct health cost of PAEs (in 2015 Euros) for each of the 30 nations as well as for their total is presented in Table 2. The cost of PAEs for the 30 nations is estimated to be between 1.1 and 2.43% of THE, and thus lie in the range of 17–38 billion Euros for the total of the 30 nations in 2015. The total annual DALYs caused by AEs in this population were calculated as 3.5 million DALYs, of which 1.5 million were assumed to have been preventable (Table 3).

Discussion

The human burden associated with AEs is well established [5] and also represents a relevant cost in economic terms. In this study, a literature-based evaluation was conducted to estimate the costs of PAEs to 30 European nations. We estimated the annual cost of PAEs to be in the range of 17–38 billion Euros, total DALYs lost from AEs as 3.5 million, of which 1.5 million DALYs were likely due to PAEs. Our findings emphasize the large costs of AEs to healthcare systems and possible savings to be made from preventing them. Patient safety is priority to most healthcare systems. And the Joint Action European Union Network for PaSQ is one of the many initiatives designed to improve the patient safety. PaSQ facilitates information sharing and the implementation of good patient safety practices among member states to reduce the risk of healthcare-related AEs.

The figures from our economic analysis need to be put into the context of disease burden. The total of the THE costs for the 30 European nations included in this study was €1578 billion. Respiratory diseases alone costs the EU (directly and indirectly) over €380 billion annually [35]. Our estimate of the cost of PAEs ranges from €17 billion to €38 billion. While this cost appears to be small in comparison, it nevertheless represents a substantial cost that healthcare systems could avoid. Extrapolating the cost of PAEs is problematic, given the limitations of available published literature, i.e. the lack of clear reporting of costing methodology and where

Table 2 Estimates of the direct health costs of PAEs

Country	Population[a]	GDP US$	THE			Direct health costs of PAEs	
		per country[b]	as % of GDP[c]	in US$ based on GDP data of the year	in Euros[d] based on GDP data of the year	in Euros (assuming PAE costs = 1.1% THE[e])	in Euros (assuming PAE cost = 2.43% THE[f])
	2015 (millions)	2015 (billions)	2013 (%)	2015 (billions)	2015 (billions)	2015 (millions)	2015 (millions)
Austria	8.545	374.1	11.0	41.15	37.1	408.3	901.9
Belgium	11.299	454.7	11.2	50.92	45.9	505.2	1116.1
Bulgaria	7.150	49.0	7.6	3.72	3.4	36.9	81.5
Croatia	4.240	48.9	7.3	3.57	3.2	35.4	78.2
Cyprus	1.165	19.3	7.4	1.43	1.3	14.2	31.4
Czech Rep.	10.543	181.9	7.4	13.42	12.1	133.1	294.1
Denmark	5.669	295.0	10.6	31.26	28.2	310.2	685.2
Estonia	1.313	22.7	5.7	1.29	1.2	12.8	28.4
Finland	5.503	229.7	9.4	21.59	19.5	214.2	473.1
France	64.395	2421.6	11.7	283.32	255.5	2810.8	6209.3
Germany	80.689	3357.6	11.3	379.41	342.2	3764.1	8315.2
Greece	10.955	195.3	9.8	19.14	17.3	189.9	419.5
Hungary	9.855	120.6	8.0	9.65	8.7	95.7	211.5
Ireland	4.688	238.0	8.9	21.18	19.1	210.2	464.3
Italy	59.798	1815.8	9.1	165.23	149.0	1639.3	3621.3
Latvia	1.971	27.0	5.7	1.54	1.4	15.3	33.8
Lithuania	2.878	41.3	6.2	2.56	2.3	25.4	56.1
Luxembourg	0.567	57.4	7.1	4.08	3.7	40.4	89.4
Malta	0.419	9.8	8.7	0.86	0.8	8.5	18.8
Netherlands	16.925	738.4	12.9	95.26	85.9	945.0	2087.6
Norway	5.211	389.5	9.6	37.39	33.7	370.9	819.5
Poland	38.612	474.9	6.7	32.01	28.9	317.5	701.5
Portugal	10.350	199.1	9.7	19.31	17.4	191.6	423.2
Romania	19.511	177.3	5.3	9.40	8.5	93.2	206.0
Slovakia	5.426	86.6	8.2	7.10	6.4	70.5	155.7
Slovenia	2.068	42.8	9.2	3.93	3.5	39.0	86.2
Spain	46.122	1199.7	8.9	106.77	96.3	1059.3	2340.1
Sweden	9.779	492.6	9.7	47.78	43.1	474.1	1047.2
Switzerland	8.299	664.6	11.5	76.43	68.9	758.2	1675.0
UK	64.716	2849.3	9.1	259.29	233.9	2572.4	5682.7
Totals	518.661 million people			$1750.03 billion	€1578.3 billion	€17 361.8 million	€38 353.9 million

[a]UN Department of Economic and Social Affairs [16].
[b]IMF [17].
[c]WHO [15].
[d]ECB average historical currency exchange rate 2015 (1 US$ = 0.9019 Euros) [18].
[e]1.1% estimate used for incremental PAE costs according to Thomas *et al.* [12] and Hoonhout *et al.* [3].
[f]2.43% estimate used for incremental PAE costs according to Antoñanzas [13].

Table 3 Estimate of DALYs lost for PaSQ nations plus Switzerland

Population PaSQ nations plus Switzerland 2015 millions[a]	Hospitalizations per year[b] (×10.8%) millions	AEs per year[c] (×14.2%) millions	DALYs lost per year[d] (×44.4%) millions	Preventable DALYs per year[e] (×43.5%) millions
518.661	56.015	7.9542	3.532	1.536

[a]Population total for PaSQ nations plus Switzerland, 2005: UN Department of Economic and Social Affairs [16].
[b]Rate of hospitalization for the high-income countries [5].
[c]Rate of AEs per hospitalization for the high-income countries [5].
[d]Rate of DALYs per AEs in the high-income countries (7.2/16.2) [5].
[e]Estimate of AEs that are preventable [10].

reported, the wide variations in the methods for attributing costs [36, 37]. In addition, the majority of published studies are in acute care, but considering the high degree of uncertainty about AEs in primary care and mental health, any estimates of the overall cost of AEs or PAEs have to make considerable assumptions. Therefore, the total costs of PAEs within any jurisdiction can only be estimated. Moreover, the majority of the studies assessed the clinical burden of AEs, but not other costs related to AEs, such as financial

compensations to patients for injuries, loss of earnings or reduced quality of life. Therefore, published figures of the economic impact of AEs in Europe are limited to the burden of healthcare.

Although there are different instruments and approaches for assessing the preventability of ADEs [38], such as the one by Schumock and Thornton [39], so far there is no single standardized instrument for identifying and costing AEs that would permit direct comparisons among the studies reviewed for this paper. However, the methodology of many recent studies is based upon the two-stage retrospective record review technique [1] in which two physicians independently reviewed cases using standardized checklists and using a 6-point scale to identify if a case is an AE and decide on its preventability. Two studies [3, 12] used the Harvard Study's definitions, standardized procedures for identifying AEs and assessing preventability. The other two studies [13, 14] derived cost estimates for AEs from a Spanish national medical database, coded cases according to standardized criteria and identified AEs using the Patient Safety Indicators of the Agency for Healthcare Research and Quality [40], and indicators of the EuroDRG project.

Limitations

An initial literature review informed our economic analysis, and although we searched multiple databases for all pertinent articles about the topic, critically appraised the literature and used a methodical approach to group-related studies, we did not follow the formal processes used in the systematic reviews. Therefore, our selection of included studies may be biased and studies with lower methodological quality may have been included.

Also, estimates from our analysis should be considered in the context of the following limitations. First, due to a dearth of suitable European studies, our analysis was based on the assumption that the AEs experienced by patients in all EU countries are similar. For this reason, we used the data reported in some EU countries to extrapolate and inform the financial implications of AEs in other countries, where data were unavailable. Second, because our extrapolations to estimate the costs of PAEs in the 30 European countries were done from data in only three studies—two from Spain and one from the Netherlands, we have estimated only a possible range of PAE costs (rather than fixed values) and this range of values should be considered as preliminary. Third, most of the studies did not judge the preventability of AEs at all, or did not provide any costing information for PAEs. Thus, it was not possible for us to make detailed and informed comparisons of the costs in various countries. However, there was enough information provided in three studies [3, 13, 14] for us to make preliminary estimates of PAE costs for the 30 nations. With the understanding that the available data are too variable to calculate a precise cost of PAEs, we have attempted only to indicate the broad dimension of the problem. Thus, our approach has been to calculate an estimate of the lower and upper margins of these costs, while erring on the conservative side.

In addition, the degree of confidence that can be placed in the estimates for the upper and lower margins of the range is limited in at least three ways. First, the three studies do not include the same set of costs, though for in-hospital costs, the types of costs included and the methodology used were quite similar. Second, because healthcare systems have different distributions of hospital and non-hospital treatment costs, it cannot be assumed that the ratio that Hoonhout *et al.* [3] reported for the Netherlands would apply in other European nations. However, from a more detailed analysis of the cost information, it can be assumed that the 1.1% lower estimate for PAE costs is conservative. Similarly, the 2.43% estimate for the upper margin may be too low because the assumptions made in its calculation were too conservative. Third, the estimate for the 2.43% upper margin rests on the simple assumption that the average costs for AEs and PAEs are similar; no information is available to support or refute this assumption. Further details of our assumptions and calculations are provided in the Supplementary material.

Patient safety interventions are possible strategies for decreasing PAEs. These can be 'soft' strategies, i.e. systematic process measures such as the use of checklists or hard measures such as removing certain high-risk medicines form ward areas or using non-compatible connectors. Unfortunately, economic evaluations of patient safety initiatives are often burden studies [3, 5, 20, 22] and there are not many complete evaluations from the EU countries to establish the relationship between costs of resources for patient safety improvement and the obtained outcomes [36]. Therefore, efforts to develop and implement patient safety improvements are complicated by uncertainties of the economic impact of AEs and also by the lack of clarity about which improvement strategies would offer the best value [41].

Conclusion

In conclusion, the economic burden of AEs and PAEs is substantial. Considering that the cost of PAEs to the EU lies in the range of 17–38 billion Euros per annum, any potential savings due to the implementation of effective patient safety practices are likely to be significant, although whether interventions will be 'cost saving' will depend on the effectiveness and the costs of the interventions. Therefore, further cost effectiveness studies from Europe are warranted in all care settings, to better appreciate the economic benefits of patient safety interventions.

Supplementary material

Supplementary material is available at *International Journal for Quality in Health Care* online.

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